AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 08: Functional Limitations and Disability

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. HHSA290201000006C

Prepared by:
ECRI Institute
5200 Butler Pike
Plymouth Meeting, PA 19462

December 2012

Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

Disclaimer Regarding 508-Compliance

Individuals using assistive technology may not be able to fully access information in this report. For assistance contact info@ahrq.gov.

Financial Disclosure Statement

None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

Public Domain Notice

Suggested citation: ECRI Institute. AHRQ Healthcare Horizon Scanning System Potential High-Impact Interventions: Priority Area 08: Functional Limitations. (Prepared by ECRI Institute under Contract No. HHSA290201000006C.) Rockville, MD: Agency for Healthcare Research and Quality. December 2012. http://www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High Impact report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Elise Berliner, Ph.D.
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Contents

Figures

Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identifying new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 7 years out on the horizon and then to follow them for up to 2 years after initial entry into the health care system. Since that implementation, review of more than 15,000 leads about potential topics has resulted in identification and tracking of about 1,600 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 950 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice annually. Topics eligible for inclusion are those interventions expected to be within 0–4 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the seven or eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts' rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of "lower," "moderate," or "higher" within the potential high-impact range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received, and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ's Effective Health Care Web site.

Results

The table below lists the 22 topics for which (1) preliminary phase III data were available for drugs being developed for labeled indications or at least phase II data were available for devices, off-label drugs, or biologics; (2) information was compiled by October 26, 2012, in this priority area; *and* (3) we received six to nine sets of comments from experts between January 13, 2011, and October 19, 2012. (A total of 179 topics in this priority area was being tracked in the system as of October 26, 2012.) We present nine summaries on nine topics (indicated below by an asterisk) that emerged as having high-impact potential on the basis of experts' comments.

Priority Area 08: Functional Limitations and Disability

Topic	High-Impact Potential
1. Aflibercept for treatment of wet, age-related macular degeneration	No high-impact potential at this time
2. Bupivacaine extended-release liposome injection (Exparel) for treatment of postsurgical pain	No high-impact potential at this time
3. * Computerized walking systems (ReWalk and Ekso) for patients with paraplegia from spinal cord injury	Moderately high
4. * Dimethyl fumarate (BG-12, Panaclar) for treatment of relapsing-remitting multiple sclerosis	High
5. Dopamine stabilizer pridopidine (Huntexil, ACR16) for treatment of Huntington's disease	No high-impact potential at this time
6. * Ezogabine (Potiga) for treatment-resistant, partial-onset epilepsy	Moderately high
7. Gel polymer (LeGoo) for prevention of blood loss in vascular surgery	No high-impact potential at this time
8. Glutamate receptor antagonist (perampanel) for treatment of partial-onset epilepsy	No high-impac potential at this time
9. * Icatibant (Firazyr) for treatment of acute hereditary angioedema	High
10. * Intraoral tongue-drive computerized system to maneuver electrically-powered wheelchairs	Moderately high
11. Micro-bypass implant (iStent) for treatment of glaucoma	No high-impact potential at this time
12. * Nasha/Dx, Solesta for treatment of fecal incontinence	High
13. Neurostimulation (remedē System) for treatment of central sleep apnea associated with heart failure	No high-impact potential at this time
14. * OBI-1 for treatment of acquired hemophilia A	Moderately high

Topic	High-Impact Potential
15. Oral growth hormone secretagogue (AEZS-130) for diagnosis of adult growth hormone deficiency	No high-impact potential at this time
16. * Orally inhaled dihydroergotamine (Levadex) for treatment of migraine headache	Lower end of the potential high-impact range
17. PTH (1-84) for treatment of hypoparathyroidism	No high-impact potential at this time
18. * Recombinant human ocriplasmin (Jetrea) injection for treatment of focal vitreomacular adhesion	High
19. Sumatriptan iontophoretic patch (Zelrix) for treatment of acute migraine headache	No high-impact potential at this time
20. Taliglucerase alfa for treatment of Gaucher's disease	No high-impact potential at this time
21. Terlipressin for reversal of hepatorenal syndrome type 1	No high-impact potential at this time
22. UroLift system for treatment of lower urinary tract symptoms caused by benign prostatic hyperplasia	No high-impact potential at this time

Discussion

The AHRQ priority area of functional limitations encompasses a wide range of disease states and conditions that affect peoples' ability to function normally, including autoimmune diseases, hematologic diseases, conditions causing chronic pain, degenerative diseases, central and peripheral nervous system disorders, physical limitations incurred because of spinal cord injury, sensory conditions (sight, hearing, touch, taste, smell), sleep disorders, organ failure (other than heart), and certain genetic disorders that are outside of the other priority areas. The material on interventions in this Executive Summary and the report is organized alphabetically by disease state, and then by interventions. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

Central Nervous System Disorder Intervention

Dimethyl Fumarate (BG-12, Panaclar) for Treatment of Relapsing-Remitting Multiple Sclerosis

- **Key Facts**: Multiple sclerosis (MS) is a progressive autoimmune disorder directed against the central nervous system (CNS). Even with available treatments, inflammation and subsequent damage to the spinal cord and brain interfere with a variety of functions, which can eventually lead to the need for institutional long-term care. Relapsing-remitting multiple sclerosis (RRMS) is the most common form. First-line therapies consist of injectable immunomodulators that dampen autoimmune responses against the CNS. These include interferon beta-1b, interferon beta-1a, glatiramer acetate, and the recently approved oral therapy fingolimod (Gilenya™). A drug in development, dimethyl fumarate (Panaclar™, Biogen Idec International GmbH, Zug, Switzerland) is an oral fumaric acid ester purported to induce both anti-inflammatory and neuroprotective effects through upregulating the transcription factor Nrf2. In phase III clinical trials, dimethyl fumarate reduced the frequency of relapse, the number and progression of brain lesions, and rate of disability progression in patients with RRMS. Dimethyl fumarate is being studied as both monotherapy and adjunctive therapy. The most common adverse events reported in clinical studies included decreased lymphocyte counts, diarrhea, flushing, gastrointestinal symptoms, headache, and a mild increase in liver enzymes. The manufacturer submitted a new drug application (NDA) to the U.S. Food and Drug Administration (FDA) in February

2012 for treating RRMS. In May 2012, FDA accepted the NDA, and a decision was scheduled for late 2012. In October 2012, FDA announced a 3-month postponement, and a decision is now anticipated in March 2013.

- **Key Expert Comments**: The experts commenting on this topic stated that a well-tolerated oral agent with high efficacy in patients with RRMS continues to present a significant unmet medical need, despite other recent drug approvals for RRMS treatment. Experts were encouraged by the lower rates of relapse and delayed disease progression reported in patients treated with dimethyl fumarate as well as the drug's tolerability profile. In other comments on competing drug fingolimod, experts stated that fingolimod, the first oral agent approved to treat RRMS, was expected to have wide acceptance among clinicians and patients, although costs (estimated at $48,000 per patient per year) and the adverse event profile could pose some barriers to diffusion. Two other orally administered MS drugs in phase III development, teriflunomide and laquinimod, have differing mechanisms of action and are being tracked in the system. However, experts commenting on these other drugs in development did not view them as having potential for high impact because, the experts stated, the unmet need these two agents address has been addressed by fingolimod. Experts commenting on dimethyl fumarate cited its high efficacy, safety, and purported neuroprotective effects as potentially addressing unmet needs in MS therapy. If dimethyl fumarate can reduce disease progression and the need for assistance with activities of daily living and have a cost comparable to current first-line agents, if approved, it could become the first-line therapy of choice for patients, clinicians, and third-party payers.
- **Potential for High Impact**: High

Epilepsy Intervention

Ezogabine (Potiga) for Treatment-Resistant, Partial-Onset Epilepsy

- **Key Facts**: Partial-onset seizures are the most commonly occurring seizure type in patients with epilepsy. According to the Epilepsy Foundation, about 20% of patients with epilepsy do not respond to available pharmacotherapy, and these patients might need invasive surgical resection or implantation of a vagus nerve stimulator. Therefore, a novel, effective pharmacotherapy would address an important unmet need. Ezogabine (Potiga, also known as retigabine, Valeant Pharmaceuticals International, Inc., Montreal, Quebec, Canada, and GlaxoSmithKline, Middlesex, UK) is an anticonvulsant purported to act as both a potassium- channel opener and a gamma aminobutyric acid potentiator. It represents a new mechanism of action for this indication. The drug has been investigated as adjunctive therapy for treatment-resistant epilepsy characterized by partial-onset seizures. After more than 18 months under FDA consideration, including FDA's issuance of a complete response letter in 2010 citing nonclinical reasons for not approving the drug, FDA approved the drug in June 2011 as an add-on medication to treat seizures associated with epilepsy in patients 18 years of age or older. The dosage is titrated over time starting at 300 mg per day (100 mg tablets thrice daily), and the maximum recommended dosage is 1,200 mg per day (400 mg tablets thrice daily). As a condition of approval, FDA recommended the drug be listed under the Controlled Substances Act, which delayed its availability for several months. FDA approval also required a Risk Evaluation and Mitigation Strategy to inform health care professionals who prescribe the drug of the risk of urinary retention and the symptoms of acute urinary retention. Additionally, FDA published information warning patients about risks of neuropsychiatric symptoms, including confusion, hallucinations, psychotic

symptoms, and suicidal thoughts. Dosage is titrated over time starting at 300 mg per day, and the dosage required varies by patient, with a maximum recommended dosage of 1,200 mg daily. The drug comes in 50-, 200-, 300-, and 400-mg tablets. At the time of this report, the cost of 30 50-mg tablets listed at 25 different retail pharmacies was between $111 and $115 and the cost of 30 400-mg tablets was between $218 and $221, when available discount coupons were used. Thus, the cost of treatment for 30 days would be about $660. Many third-party payers have added the drug to their formularies and require prior authorization and quantity limits.

- **Key Expert Comments**: Overall, experts commenting on this topic were optimistic about the drug's potential to meet the need for an effective new pharmacotherapy for this patient population because of its novel mechanism of action and the clinical trial data thus far. As an oral drug, it could be incorporated easily into the existing care model for epilepsy. If the drug can reduce seizures by nearly 50% and obviate the need for invasive interventions, most experts thought, it could affect several health system parameters by shifting the care setting and patient management to the physician office and home setting, thereby reducing treatment costs and improving patient quality of life.
- **Potential for High Impact**: Moderately high

Gastrointestinal Disorder Intervention

Nasha/Dx, Solesta for Treatment of Fecal Incontinence

- **Key Facts:** Available therapy for fecal incontinence has limited efficacy and is invasive or associated with adverse events, marking a need for more innovative interventions. Nasha™/Dx (Solesta®; Oceana Therapeutics, Inc., Edison, NJ), is a biocompatible tissue-bulking agent consisting of cross-linked dextran chain microspheres, with dextran biosynthesized by fermentation of the bacteria *Leuconostoc mesenteroides* and stabilized sodium hyaluronate buffered in a sodium chloride solution. Nasha/Dx can be administered on an outpatient basis in a physician's office via injection (dextranomer microspheres, 50 mg/mL; stabilized sodium hyaluronate, 15 mg/mL; in phosphate buffered 0.9 % sodium chloride solution) in the deep submucosal layer of the proximal anal canal. In May 2011, FDA approved Nasha/Dx for treating fecal incontinence in adult patients whose disease is refractory to conservative, traditional therapies. In September 2011, Oceana Therapeutics launched Nasha/Dx in the United States. The average wholesale price of Solesta is reported as $1,107 per 1 mL injection or $4,428 per treatment session. Re-treatment is sometimes required and is intended to occur no sooner than 4 weeks after the initial procedure. The procedure is covered by several third-party payers.
- **Key Expert Comments:** Overall, experts commenting on this intervention saw a particular need for more effective therapy for fecal incontinence and minimally invasive treatment. Several experts opined that this intervention has potential to improve patient health, quality of life, and help patients avoid surgical intervention. Experts saw a potential shift from inpatient surgical management to outpatient management.
- **Potential for High Impact:** High

Genetic Disorder Intervention

Icatibant (Firazyr) for Acute Hereditary Angioedema

- **Key Facts:** Acute hereditary angioedema (HAE) results from a genetic disorder caused by dysfunction or deficiency of C1 esterase inhibitor (C1INH), an inhibitor of the C1 protease that is responsible for activating the complement pathway of the innate immune system. If C1INH is deficient, an acute inflammatory response occurs that leads to swelling that is the hallmark of HAE. Attacks involving the larynx can be fatal; serious attacks are associated with a mortality rate of 15% to 33%. Abdominal attacks can also cause severe pain and disfigurement. Each bout of edema can last 3–5 days; the trigger for attacks is unknown. Icatibant (Firazyr®, Shire, plc, Dublin, Ireland) is a bradykinin receptor-2 antagonist that was approved by FDA in August 2011 as the only injectable drug to treat acute HAE that can be self-administered by the patient. Thus, icatibant allows patients to manage this lifelong condition on an outpatient basis. In phase III trials, icatibant provided significant relief of symptoms within about 2 hours and initial symptom relief in less than 1 hour. The average wholesale cost of this drug in the United States is about $8,400 per dose. The company's Quick Start program and extended OnePath Access Program were created to offer product-related services and support to patients. After a health care provider prescribes the drug, patients can enroll to be eligible to receive two syringes of the drug at no cost. In general, third-party payers cover icatibant for patients with type I and II HAE, generally requiring preauthorization and prescription by a specialist and enforcing quantity limits.
- **Key Expert Comments**: Overall, experts commenting on icatibant viewed it as having significant potential to shorten the duration of symptoms and improve clinical outcomes in the small number of patients with HAE, a potentially life-threatening condition. Experts noted that although other, new treatments have just become available for HAE, icatibant has a different mechanism of action and may be self-administered on an outpatient basis, which could significantly minimize hospitalizations and the role emergency personnel play in managing HAE in a subset of patients.
- **Potential for High Impact**: High

Hematologic Disorder Intervention

OBI-1 for Treatment of Acquired Hemophilia A

- **Key Facts**: Currently, an estimated 20,000–25,000 individuals have some type of hemophilia in the United States, with acquired hemophilia affecting from 1 to 4 individuals (primarily middle-aged individuals) per million. Current therapies, specifically human factor VIIa (NovoSeven®) and Feiba™, work by bypassing the coagulation cascade, producing extremely higher-than-normal levels of factor VIIa to induce coagulation. However, no available therapies address the underlying pathogenesis of acquired hemophilia, in which autoantibodies produced against the body's coagulation factors result in excessive bleeding episodes. OBI-1 (Inspiration Biopharmaceuticals, Inc., Cambridge, MA, and Ipsen, Paris, France) therapy is an intravenous recombinant porcine factor VIII product that serves as factor VIII replacement therapy by activating the natural coagulation cascade. OBI-1 was given orphan drug status by FDA in March 2004; the European Commission also granted orphan drug status for OBI-1 for treating hemophilia. A phase II/III trial began in 2010 for acquired hemophilia and is ongoing. A phase III trial started in late 2011 to treat hemophilia A (congenital hemophilia) is ongoing. Inspiration Biopharmaceuticals filed for chapter 11

bankruptcy in October 2012, and worldwide rights to OBI-1 development have been acquired by Ipsen.

- **Key Expert Comments**: Overall, experts commenting on this intervention were generally optimistic about OBI-1 therapy's potential to meet the need of patients who experience complications from acquired hemophilia, highlighting its apparently sound mechanism of action. Experts commenting on this drug generally believe that if efficacy is confirmed in pivotal trials, OBI-1 therapy has the potential to control acute bleeding symptoms for patients with acquired hemophilia and may subsequently alter treatment models.
- **Potential for High Impact**: Moderately high

Pain Intervention

Orally Inhaled Dihydroergotamine (Levadex) for Treatment of Migraine Headache

- **Key Facts**: Migraine headache affects an estimated 28 million people each year in the United States. Many patients are dissatisfied with their current migraine medication because of an inconsistent response, migraine recurrence after treatment, and/or slow onset of action in relieving pain. Therefore, new treatments for migraine headache are highly desired. One long-available migraine treatment is the ergot alkaloid dihydroergotamine (DHE). DHE has been available as an injectable solution and nasal spray. A new DHE formulation is in development, Levadex® (MAP Pharmaceuticals, Inc., Mountain View, CA) as an orally inhaled formulation that is delivered using the developer's proprietary Tempo™ breath-activated metered dose inhaler. Compared with injectable DHE, Levadex is purported to be more convenient, faster-acting, and associated with fewer side effects. It might also avoid the local nasal irritation and inconsistent absorption that have been observed with nasal spray delivery. In August 2011, MAP Pharmaceuticals filed an NDA for Levadex for treating migraine headache, and FDA accepted the filing. In March 2012, FDA issued a complete response letter requesting that the manufacturer address issues relating to chemistry, manufacturing, controls, and a facility inspection at a third-party manufacturer. The manufacturer planned to meet with FDA to address issues raised in the complete response letter. In October 2012, the manufacturer resubmitted the NDA for Levadex to FDA and on November 21, 2012, announced that FDA had classified the resubmission as complete.
- **Key Expert Comments**: Overall, experts providing comment on the DHE formulation thought a significant unmet need still exists for improved migraine treatment and that an inhaled DHE formulation that would allow fast, easy, and effective self-administration could address that need. Experts generally agreed that Levadex has potential to significantly improve pain outcomes more than that achieved by current DHE formulations. However, several experts were concerned about the potential side effects and opined that the potential clinical acceptance may be affected by the overall safety of this intervention.
- **Potential for High Impact**: Lower end of the potential high-impact range

Sensory Disorder Interventions

Recombinant Human Ocriplasmin (Jetrea) Injection for Treatment of Focal Vitreomacular Adhesion

- **Key Facts**: Current treatment options for symptomatic vitreomacular adhesion are limited to invasive vitreoretinal surgical procedures that are associated with serious side effects of risk of incomplete vitreoretinal separation and/or removal, surgical complications (e.g., development of cataracts), and high costs. Recombinant ocriplasmin (Jetrea®, ThromboGenics NV, Heverlee, Belgium) is a minimally invasive option. It retains the catalytic characteristics of human plasmin and is purported to have several advantages, including being sterile because of recombinant techniques used to generate it, being smaller in size than plasmin to potentially allow greater penetration of epiretinal tissues, and being more stable than plasmin. Investigators reported that two phase III trials with 652 patients at 90 centers in Europe and the United States met their primary endpoints. FDA approved ThromboGenics' biologics license application (BLA) for ocriplasmin in October 2012, for treating symptomatic vitreomacular adhesion.
- **Key Expert Comments**: Experts thought recombinant ocriplasmin injection therapy would offer an alternative to surgical intervention for patients most affected by focal vitreomacular adhesion. They generally agreed that the potential acceptance would be high for clinicians and patients alike. Most experts who commented thought that ocriplasmin injection therapy could provide an effective, cost-saving alternative to current standard treatment.
- **Potential for High Impact**: High

Spinal Cord Injury Interventions

Computerized Walking Systems (ReWalk and Ekso) for Patients with Paraplegia from Spinal Cord Injury

- **Key Facts**: Conventional manual and powered wheelchairs are the primary assistive devices to restore some degree of mobility in people with paraplegia. However, these devices do not assist users in walking or climbing stairs. Two reciprocating gait orthosis systems in development, the ReWalk-I™ system (Argo Medical Technologies, Ltd., Yokneam Ilit, Israel) and the Ekso™ system (formerly eLegs, Ekso Bionics, Richmond, CA), are providing greater mobility and freedom to people with paraplegia from spinal cord injury. The ReWalk system comprises a set of computer-controlled, motorized leg braces that restore the ability to walk with crutches to patients with paraplegia who retain the ability to use their hands and shoulders and who have good bone density and cardiovascular health. The Ekso system incorporates technology similar to that of the ReWalk system. FDA classifies the ReWalk system as powered exercise equipment used for medical purposes (e.g., physical therapy), thus making the technology exempt from 510(k) premarket notification and premarket application procedures. The ReWalk-I (institutional use) system is currently FDA-listed for institutional use only, and reported costs are about $105,000 per system. The company expected to register the ReWalk-P system for personal use with FDA in the near future. The company has been quoted in lay press articles as stating that the personal system will cost one-third to one-half that of an institutional system. The Ekso institutional system first became available in February 2012 and costs an estimated $130,000, with anticipated costs for a personalized Ekso exoskeleton version estimated to be $50,000–$75,000.

- **Key Expert Comments**: Experts thought that this equipment could offer independence currently not available to these patients. However, they thought the high cost and complexity of this technology could limit its introduction and diffusion into the mainstream of rehabilitative services for patients with paraplegia from spinal cord injury. Staffing models would be affected by the need for clinical and software engineers and technicians to maintain and adjust the equipment. Also, the equipment would likely be appropriate only for patients whose health is robust enough to use it. Experts indicated that the intended population has very limited treatment options, and they agree upon the vast potential benefit of computerized walking systems.
- **Potential for High Impact**: Moderately high

Intraoral Tongue-Drive Computerized System to Maneuver Electrically-Powered Wheelchairs

- **Key Facts**: Although conventional manual and powered-assisted devices exist that attempt to improve quality of life for individuals with paraplegia, efficacy and safety issues remain a primary concern. The Tongue Drive System (TDS, Georgia Institute of Technology, Atlanta) is a tongue-operated, assistive neurotechnology that consists of a lentil-sized magnetic tracer/stud that is embedded in a dental retainer worn in the mouth with the tracer affixed to the tongue, most commonly by piercing. This magnetic tracer communicates synergistically with a headset, magnetic sensors, and a smartphone device to increase patient mobility and allow patients to participate in daily activities. Use of the system would represent a way to purportedly enhance patient mobility and allow patients to perform more daily tasks in a safer, less invasive, and more effective manner than afforded by existing devices. Patients must undergo computer training with the TDS for the computer program to appropriately interpret and calibrate tongue movement, allowing for proper control of the patient wheelchair and computer device. The TDS is in early-phase clinical trials in two locations (Atlanta, GA, and Chicago, IL), and the trial continues to recruit patients. About 20 patients have been reported to have trialed the system thus far. The National Science Foundation, the Christopher & Dana Reeve Foundation, and the National Institute of Biomedical Imaging and Bioengineering at the National Institutes of Health are providing funding to support development of the system.
- **Key Expert Comments**: Experts commenting on this intervention had diverse perspectives about some aspects, although most thought that the system could be a viable alternative to existing technologies. Some thought the unmet need was not significant, but other experts who have worked directly with spinal cord injured patients in need of assistive devices to control powered wheelchairs saw this intervention as a significant improvement for patient health outcomes and quality of life, allowing patients to perform daily activities in a quicker and less exhaustive manner than existing technologies such as puff-straws, joysticks, and head-paddles. Several experts thought safety concerns could be a barrier to clinician acceptance, because device malfunction could introduce harm to this patient population. Overall, this device's perceived complex nature, the existence of alternatives, and limited safety and efficacy data thus far have made some experts question the device's true impact potential. However, other experts believe this device has the ability to significantly improve patient mobility and quality of life when compared with standard mobility devices.
- **Potential for High Impact**: Moderately high

Central Nervous System Disorder Intervention

Dimethyl Fumarate (BG-12, Panaclar) for Treatment of Relapsing-Remitting Multiple Sclerosis

Multiple sclerosis (MS) is a common cause of physical disability in the United States.[1] Inflammation damages the myelin surrounding nerves, impeding the electrical impulses that travel along the nerves. As the disease progresses, it eventually causes interference with vision, speech, walking, writing, memory, sexual function, and bowel and bladder control.[2,3] Relapsing-remitting multiple sclerosis (RRMS) is the most common form of MS and is usually the earliest form to be diagnosed.[4] First-line therapies consist of injectable immunomodulators that dampen autoimmune responses against the central nervous system (CNS). Oral fingolimod became available in 2010.[5] However many patients' RRMS symptoms do not respond adequately to current therapies or patients are unable to tolerate the treatments, and no effective treatments are available to stop the long-term progression of the disease.[4,6-8]

Dimethyl fumarate (BG-12, Panaclar™, Biogen Idec International GmbH, Zug, Switzerland) is an orally administered, homogenous fumaric acid ester formulation that is purported to have immunomodulatory and neuroprotective effects. Dimethyl fumarate is purported to increase expression of Nrf2, a transcription factor known to upregulate cellular antioxidant pathways. The increased expression and upregulation results in changes in the cellular redox system leading to an increase in reduced glutathione and intracellular glutathione, which could protect neurons and astrocytes from oxidative stress during inflammatory processes.[9,10] These changes are also purported to inhibit nuclear factor kappaB translocation and downstream proinflammatory signaling.[11] These anti-inflammatory and neuroprotective effects are purported to reduce the number of active brain lesions that could contribute to disease progression.[12] Dimethyl fumarate has been administered at a dosage of 240 mg twice and three times daily in clinical trials and is being investigated as monotherapy and adjunctive therapy.

In two randomized, multicenter, phase III trials, the effects of BG-12 were evaluated in patients with RRMS. In one trial, the investigators reported on patients (n=1,237) who received 240 mg of dimethyl fumarate either two or three times daily for 24 months. Results demonstrated a statistically significant reduction in the proportion of patients whose disease relapsed at 2 years compared with patients given placebo (27% and 26% for dimethyl fumarate twice and three times daily, respectively, vs. 46% with placebo; $p<0.001$ for both comparisons). Patients given both doses of dimethyl fumarate also demonstrated statistically significant reductions in secondary endpoints including annualized relapse rate (53% and 48% for twice and three times daily, respectively; $p<0.001$ for both), the number of new or newly enlarging T2 hyperintense lesions seen on magnetic resonance imaging scans (85% and 74% for twice and three times daily, respectively; $p<0.001$ for both), and the mean number of new gadolinium-enhancing lesions, (90% and 73% for twice and three times daily, respectively, $p<0.001$ for both), compared with those results achieved by administering placebo. Patients given either dose of dimethyl fumarate also exhibited a significant reduction in the rate of disability progression as measured by the Expanded Disability Status Scale. Adverse events associated with dimethyl fumarate included "diarrhea, decreased lymphocyte counts, elevated liver aminotransferase levels, flushing, nausea, and upper abdominal pain."[12]

In the second study, investigators reported that patients with RRMS (n=1,430) who received 240 mg of dimethyl fumarate either twice or three times daily for 24 months had significant reductions in annualized relapse rate (44%, and 51% for dimethyl fumarate twice and three times daily, respectively; $p<0.0001$ for both) compared with patients given placebo. Investigators reported that patients treated with the active comparator glatiramer acetate (20 mg subcutaneous injection, once daily) had a reduction in annualized relapse rate by 29% ($p=0.01$) compared with patients

given placebo. Additionally, investigators reported that dimethyl fumarate reduced the number of new or newly enlarging T2-hyperintense lesions by 71% and 73% for twice- and three-times-daily regimens, respectively ($p<0.0001$ for both dosage regimens) compared with placebo, while glatiramer acetate reduced lesions by 54% ($p<0.0001$ for all three treatments). Dimethyl fumarate reduced new T1-hypointense lesions by 57% and 65% for twice and three times daily, respectively ($p<0.0001$ for both dosage regimens), and glatiramer acetate reduced lesions by 41% ($p=0.002$). The proportion of patients who experienced a relapse while taking dimethyl fumarate was reduced by 34% for twice-daily dosing ($p=0.002$) and by 45% for three times daily ($p<0.0001$), compared with 29 % for glatiramer acetate ($p=0.01$). Reductions in disability progression with dimethyl fumarate twice-daily, thrice-daily, or glatiramer acetate versus placebo (21%, 24%, and 7%, respectively) were not significant.[13]

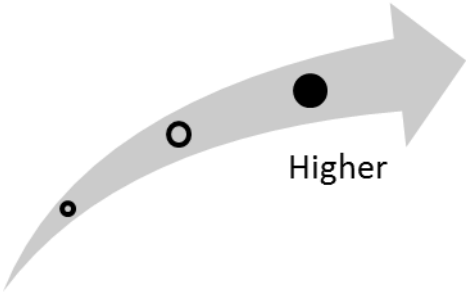
The U.S. Food and Drug Administration (FDA) granted dimethyl fumarate fast track designation in 2008.[14] In February 2012, Biogen Idec submitted a new drug application (NDA) to FDA for treating RRMS.[15] In May 2012, FDA accepted the NDA,[16] and a decision is expected in March 2013.[17]

For benchmarking purposes, the oral immunomodulator fingolimod costs about $48,000 per patient annually.[18] According to one financial analyst, as of May 2012, fingolimod represented about 5% of the MS market and injectables represented about 85% of the market.[19] Increasing acceptance and use of fingolimod and its oral competitors teriflunomide (approved September 2012[20]), dimethyl fumarate, and laquinimod (if they are approved) are expected. New agents could even bring patients back for treatment after they had discontinued previous options. However, injectables were still theorized to remain an important part of MS therapy.[19]

Clinical Pathway at Point of This Intervention

First-line treatments to reduce the frequency and severity of RRMS relapse include the injectable medications interferon beta-1b (Betaseron®), interferon beta-1a (Avonex®, Rebif®), and glatiramer acetate (Copaxone®).[4,6] Oral fingolimod is used as first- or second-line therapy. Dimethyl fumarate is intended to be used as first- or second-line monotherapy for RRMS or as an adjunct to existing therapies.

Figure 1. Overall high-impact potential: dimethyl fumarate (Panaclar) for treatment of relapsing-remitting multiple sclerosis



Experts commented that data from phase III trials are encouraging and suggest that the drug could fulfill the unmet need for a well-tolerated, oral therapy that can significantly reduce the frequency of relapse and disease progression (including brain lesions) in a majority of RRMS patients. If the drug can reduce disease progression and delay the need for assistance with activities of daily living while keeping therapy costs comparable to current first-line agents, it could become the first-line therapy of choice for patients, clinicians, and third-party payers, experts thought. Based

on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this intervention.[21-27]

Overall, the experts commented that MS is a debilitating disease that results in significant morbidity and disability. A large unmet need remains for new treatments with improved efficacy, tolerability, and ease of administration.

The experts stated that the evidence to date of dimethyl fumarate's efficacy against relapse and brain lesions compared with placebo and glatiramer acetate is encouraging, as is the favorable tolerability profile reported. Additionally, the novel mechanism of action, with potentially anti-inflammatory and neuroprotective effects, was viewed as potentially improving patient health outcomes.

Although several experts thought the high expected price of dimethyl fumarate might increase health disparities for patients without prescription coverage from a third-party payer, two experts representing a research perspective stated that patients with poor access to care, such as those in rural areas, could improve treatment adherence by being able to take a pill at home instead of traveling to a health care provider for routine injections. The experts stated that if effective in delaying disease progression and as an oral therapy that can be administered easily at home, dimethyl fumarate could reduce infrastructure and staffing needs at treatment facilities where injectables are administered as well as at long-term care facilities where patients with advanced disease receive care.

The experts stated that both clinicians and patients are expected to have a high level of acceptance of dimethyl fumarate because of the efficacy and safety profile reported in patients with RRMS. However, two experts representing a research perspective stated cost could be the major barrier to patient acceptance in cases in which patients lack adequate health insurance. The experts expected dimethyl fumarate to have a comparable cost to fingolimod or injectable therapy. If used as an adjunctive therapy, dimethyl fumarate could add significantly to costs. However, if used as monotherapy and if the drug can delay the need for institutional long-term care, the drug may be cost saving.

Epilepsy Intervention

Ezogabine (Potiga) for Treatment-Resistant, Partial-Onset Epilepsy

Partial-onset seizures are the most common form of epileptic seizures. According to the Epilepsy Foundation, about 20% of patients with epilepsy do not respond to currently available pharmacotherapy, and these patients may have to undergo invasive surgical resection or implantation of a vagus nerve stimulator. Therefore, a novel, effective pharmacotherapy would address an important unmet need for these patients.

Ezogabine (Potiga™, Valeant Pharmaceuticals International, Inc., Montreal, Quebec, Canada, and GlaxoSmithKline, Middlesex, UK) is an anticonvulsant purported to act as both a potassium-channel opener and a gamma aminobutyric acid (GABA) potentiator, representing a new mechanism of action for this indication.[28] These effects are purported to prevent the action-potential bursts that occur during the sustained depolarization observed during seizures (i.e., reducing cellular excitability).[29] In its role as a potassium-channel opener, ezogabine is purported to stabilize potassium channels in the open position, which allows the stabilizing membrane current to increase. Researchers have also suggested that ezogabine increases the concentration of GABA, the major inhibitory neurotransmitter in the brain, which has long been associated with epilepsy.[29] Ezogabine is administered as an oral tablet with an initial dosage of 100 mg three times daily and titrated up to 200–400 mg three times daily.[28] Ezogabine is also intended to be used as an adjunctive therapy with other antiepileptic pharmacotherapy.[28]

In 2011, French and colleagues presented results from a phase III trial assessing ezogabine's efficacy in 306 patients with refractory epilepsy with partial-onset seizures. The authors reported that "median percent reduction in total partial-seizure frequency was 44.3% vs 17.5% ($p < 0.001$) for [ezogabine] and placebo, respectively, during the 18-week double blind period; responder rates (≥50% reduction in total partial-seizure frequency from baseline) were 44.4% vs 17.8% ($p < 0.001$)."[30] Additionally, the authors reported that "in 256 patients ([ezogabine], 119; placebo, 137) entering the 12-week maintenance phase, median percent reduction in seizure frequency for [ezogabine] vs placebo was 54.5% and 18.9% ($p < 0.001$), respectively; responder rates were 55.5% vs 22.6% ($p < 0.001$). The proportion of patients discontinuing due to treatment-emergent adverse events was 26.8% [ezogabine] vs. 8.6% (placebo)."[30] Adverse events reported by patients treated with ezogabine in this clinical trial included "dizziness, somnolence, fatigue, confusion, dysarthria, urinary tract infection, ataxia, and blurred vision."[30] The company also reported that in its three phase III trials, "Ezogabine caused urinary retention in clinical trials. Urinary retention was reported as an adverse event in 29 out of 1,365 (approximately 2%) patients treated with ezogabine. In all studies of patients with partial-onset seizures, including open-label studies, five patients required catheterization (four on ezogabine and one on placebo). In three controlled clinical studies, 25% of patients receiving ezogabine (199/813) and 11% of patients receiving placebo (45/427) discontinued treatment because of treatment-emergent adverse reactions."[31]

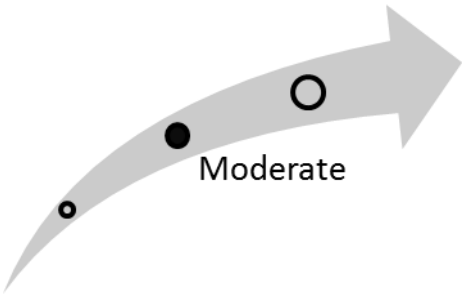
In June 2011, FDA approved ezogabine as adjunctive treatment for partial-onset seizures in adults (18 years and older).[31] FDA conditions of approval required a Risk Evaluation and Mitigation Strategy to inform health care professionals who prescribe the drug of the risk of urinary retention and the symptoms of acute urinary retention. Additionally, FDA published consumer information alerting patients to risks of neuropsychiatric symptoms, including confusion, hallucinations, psychotic symptoms, and suicidal thoughts. The drug comes in 50-, 200-, 300-, and 400-mg tablets. Product labeling recommends titrated dosing starting at 300 mg per day and increasing to a maximum of 1,200 mg per day.[28] At the time of this report, the cost of 30 50-mg tablets listed at 25 different retail pharmacies was between $111 and $115 and the cost of 30 400-mg tablets was

between $218 and $221 when available discount coupons were used. The cost of the maximum recommended dosage (1,200 mg per day) would be about $660 per month.[32,33] Many third-party payers have added the drug to their formularies and require prior authorization; they also impose monthly quantity limits.[34-39]

Clinical Pathway at Point of This Intervention

According to the Epilepsy Foundation, current treatment for this disease state includes pharmacotherapy (e.g., carbamazepine, gabapentin, phenobarbital, valproate), and, for some patients whose epilepsy is unresponsive to these agents, surgical resection or vagus nerve stimulation may be indicated. Ezogabine is FDA approved as an adjunct therapy to current antiepileptic medications and is used in concert with other epilepsy medications. Ezogabine could displace some of the need for surgical resection or vagus nerve stimulation and is expected to compete with these interventions as an option for adults with treatment-refractory epilepsy.

Figure 2. Overall high-impact potential: ezogabine (Potiga) for treatment-resistant, partial-onset epilepsy



Overall, experts commenting on this topic were generally optimistic about this drug's potential to meet the need for effective pharmacotherapy for adults with treatment-resistant, partial-onset epilepsy because of its promising mechanism of action and clinical trial data. As an oral drug, experts thought, it would be incorporated easily into the existing care model for epilepsy. However, if ezogabine obviates the need for invasive interventions for epilepsy, it would affect several health system parameters, especially those of care setting (changing to medical management rather than surgery), patient management, and treatment costs, most experts opined. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration perspectives, commented on this intervention. [40-46] These experts agreed that an unmet need exists for effective, noninvasive therapies for patients with epilepsy that is refractory to current pharmacotherapies. One clinical expert commented that surgical interventions have limited efficacy because of a relatively small surgical candidate population, thus highlighting the importance of the unmet need for new, more effective options.

Experts expressed opinions about the theory underlying the intended mechanism of action of ezogabine, with one expert stating that this mechanism could "offer the potential to increase the number of patients who can control their seizures through medication rather than surgery."[45] Experts were cautiously optimistic about the drug's potential to improve patient health outcomes, stating that although additional studies are needed to confirm efficacy and side-effects data, results so far suggest improvements in seizure rate. One expert with a health systems perspective believes

that ezogabine could offer patients greater possibility of controlling seizure rate, which in turn would positively affect patient health outcomes.

Experts stated that the drug may obviate the need for surgical resection or electrical stimulation, leading most experts who commented to believe that it has potential to shift treatment models. Similarly, by potentially reducing the need for invasive interventions, the drug has potential to shift the care setting for treatment-resistant epilepsy from an inpatient to outpatient setting, thus eliminating costs from extended hospital stays. However, some experts thought that treatment models would remain the same, because the drug is intended to be used as an oral adjunct to current pharmacotherapies.

Experts were divided on whether this intervention would increase or decrease the cost of care. Some experts claimed that costs would be reduced, because drugs are typically less expensive than surgical interventions, but others believe that, as one expert put it, "the high price would be offset by the benefit."[43] Another expert similarly noted that patients may consider this intervention to be worthwhile when taking into account its ability to control their seizures, although a long-term increase in care costs would be seen, particularly because ezogabine would be added to current oral medication regimens.

Most experts believe that both patients and clinicians would accept this intervention readily, particularly if it is shown to obviate the need for invasive procedures. One expert with a health systems perspective expressed optimism that this intervention might improve the physician-patient relationship by giving physicians another option to offer in their armamentarium.

Gastrointestinal Disorder Intervention

Nasha/Dx, Solesta for Treatment of Fecal Incontinence

Available therapies for fecal incontinence include antidiarrheal medicines and dietary and behavior therapies (to improve muscle control). Other treatment modalities for this condition include sacral nerve stimulation, surgical interventions, and an implantable silicone elastomer balloon and cuff pump, which was previously the only implantable device for this disease. These therapies have limited efficacy and are invasive and associated with adverse events, marking the need for better options.

Nasha™/Dx, Solesta® (Oceana Therapeutics, Inc., Edison, NJ), is a biocompatible tissue-bulking agent consisting of cross-linked dextran chain microspheres, with dextran biosynthesized by fermentation of the bacteria *Leuconostoc mesenteroides* and stabilized sodium hyaluronate buffered in a sodium chloride solution. The microspheres and sodium hyaluronate allow the gel to become hydrophilic and swell in water as well as swelling in the sodium chloride solution. This gel, insoluble in water and organic solvents, is intended to narrow the anal canal by expanding/bulking up the submucosal layer in the canal, thereby potentially increasing a patient's sphincter control.[47] Nasha/Dx can be injected on an outpatient basis in a physician's office (dextranomer microspheres, 50 mg/mL; stabilized sodium hyaluronate, 15 mg/mL; in phosphate buffered 0.9 % sodium chloride solution). Four injections are given in the deep submucosal layer in the proximal anal canal.[47] The injections consist of 1 mL each (4 mL total) spaced equally and close to the anorectal junction, where pain sensory innervation is minimal.

In 2011, Graf and colleagues presented results from a phase III clinical trial evaluating Nasha/Dx's efficacy in 206 patients receiving a diagnosis of fecal incontinence, in which primary endpoints included a 50% or more reduction in fecal incontinence episodes. Authors reported "71 patients who received NASHA Dx (52%) had a 50% or more reduction in the number of incontinence episode, compared with 22 patients who received sham treatment (31%; odds ratio 2·36, 95% CI [confidence interval] 1·24–4·47, p=0·0089). We recorded 128 treatment-related adverse events, of which two were serious (1 rectal abscess and 1 prostatic abscess)."[48]

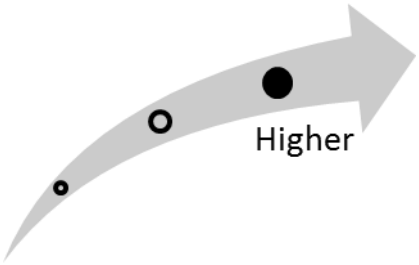
In May 2011, FDA approved the treatment for fecal incontinence in adult patients whose disease is refractory to conservative, traditional therapies.[49] In September 2011, Oceana Therapeutics launched Nasha/Dx in the United States.[49] The average wholesale price of Solesta is reported as $1,107 per 1 mL injection or $4,428 per treatment session. Re-treatment is sometimes required and is intended to occur no sooner than 4 weeks after the initial procedure. Coverage and reimbursement by third-party payers is mixed. The U.S. Centers for Medicare & Medicaid Services has no national coverage determination, and coverage is left to the discretion of local carriers. Searches of published, private, third-party payer policies identified several payers that consider treatment to be investigational, even though it has received FDA approval, and others that cover it.[50-54]

Clinical Pathway at Point of This Intervention

First-line treatment for fecal incontinence includes adherence to a high-fiber diet to improve stool consistency and better establish bowel control.[55] Alternative therapeutic measures may include antidiarrheal and dietary therapies aimed at promoting bulking of feces to allow patients to more readily control release. Behavior modifications, such as Kegel exercises, are alternative measures used to help patients control release of feces. Surgical interventions for treating fecal incontinence include sphincteroplasty, tissue ablation, and device implantation. These current pharmacologic, dietary, and nerve-stimulating therapies may not sufficiently improve fecal continence, and surgical treatments can be invasive, costly, and for some patients, result in unfavorable outcomes. Nasha/Dx

is positioned as second-line therapy for patients with fecal incontinence after traditional nonsurgical treatments have failed.

Figure 3. Overall high-impact potential: Nasha/Dx (Solesta) for treatment of fecal incontinence



Overall, experts commenting on this intervention thought that there was a particular need for more effective therapies for fecal incontinence. Several experts opined Nasha/Dx could improve patient health outcomes and quality of life and help patients avoid surgical intervention. Experts thought a potential shift from inpatient surgical management to outpatient setting would be seen. Based on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.[56-62] The experts generally agreed that an important unmet need exists for effective fecal incontinence treatment for this patient population, based on the current lack of effective therapies and their associated cost and risk of adverse events. One clinical expert opined that few patients seek proper care for fecal incontinence and that those patients who seek treatment often receive conservative treatment or no treatment at all. However, one expert opined that effective alternative therapies and "protective garments" are available for fecal incontinence management and that the need for improved options was incremental.[60]

Most experts stated this intervention has potential to improve health outcomes. Basing their opinions on preliminary results, they thought the tissue-bulking agent would not always completely resolve fecal incontinence. Most experts wanted to see additional trial results. One expert with a clinical perspective found it difficult to determine this intervention's potential to improve health outcomes, stating, "This will not work for everyone. Those with muscle disruptions will probably need surgery. Even 'perfect' candidates will sometimes not be successful."[59]

Experts generally agreed that this intervention has the potential to affect the current care model and patient management and to shift care setting from inpatient surgery to office visits. One clinical expert opined that if this treatment is proven effective, it has the potential to dramatically shift the staff needed to treat the condition, because colorectal surgeons who perform the surgical procedures would be supplanted by gastroenterologists delivering minimally invasive injections during an office visit. Another clinical expert commented on this intervention's potential to "reduce the number of individuals needed to care for incontinent patients (decreased number of aides, LPNs [licensed practical nurses], etc). It would also decrease the individual's costs for cleaning materials and local treatments (e.g. creams and ointments)."[59] One research expert added that this intervention would reduce the number of procedures performed in operating rooms.

Experts were divided on how this intervention would affect costs. Most experts commented that the gel polymer would be expensive. However, some experts also suggested that if the intervention improved patient outcomes, it would ultimately reduce long-term costs associated with invasive

surgery and inpatient care. Experts anticipated high patient acceptance of this intervention, with one clinical expert noting a patient's desperation for novel therapies to appropriately manage fecal incontinence. However, experts were divided on how likely clinicians would be to offer the therapy. One clinical expert opined, "I am not optimistic about adoption by gastroenterologists. They often do not want to care for anorectal diseases."[59] Other experts noted that this intervention might become widely accepted because it is a noninvasive alternative to surgery that would have appeal to patients.

Genetic Disorder Intervention

Icatibant (Firazyr) for Treatment of Acute Hereditary Angioedema

Hereditary angioedema (HAE) is a genetic disorder caused by dysfunction or deficiency of C1 esterase inhibitor (C1INH), an inhibitor of the C1 protease that is responsible for activating the complement pathway of the innate immune system. If C1INH is deficient, C1 proteases set off the complement pathway, causing an acute inflammatory response that leads to swelling. Part of the inflammatory response is the release of uncontrolled levels of bradykinin (BK), a potent vasodilator that acts much like a histamine.[63] During a serious attack, the patient's throat may swell and cause the airway to close, resulting in asphyxiation; this is associated with a mortality rate of 15% to 33%.[64] Abdominal attacks can also cause severe pain and disfigurement. Bouts of edema can last 3–5 days; the trigger for attacks is unknown.[63] Icatibant (Firazyr®, Shire, plc, Dublin, Ireland) is a selective and specific synthetic polypeptide BK receptor-2 (BR2) antagonist.[63,65] Preclinical study data was reported to have shown that icatibant potently and selectively inhibits BK's effects on vascular permeability, hypotension, and bronchospasm, and early clinical studies have demonstrated reversed vasodilation in humans.[63] FDA-approved in 2011 (see details below), icatibant is available as a subcutaneous injection administered 30 mg in 3 mL as needed.[65] The injection can be administered in a health care setting, most likely on the initial attack, or by the patient during subsequent attacks.

In two double-blind, randomized, multicenter trials, the effects of icatibant were evaluated in patients with HAE presenting with cutaneous or abdominal attacks.[66] In results of one trial (n=56), researchers reported that the primary endpoint of median time to clinically significant relief of symptoms was 2.5 hours compared with 4.6 hours with placebo, although the result did not reach statistical significance (p=0.14). In the second trial (n=74), researchers reported that the primary endpoint of median time to clinically significant relief of symptoms was 2 hours with icatibant versus 12 hours with tranexamic acid (p<0.001). No icatibant-related serious adverse events were reported.[66]

In 2011, data were reported from a phase IIIb trial evaluating patients who self-administered icatibant (n=88) in response to acute HAE attacks.[67] Icatibant significantly reduced the patient-assessed median time to onset of symptom relief (2.0 vs. 19.8 hours) and the median time to onset of primary symptom relief (1.5 vs. 18.5 hours) versus placebo (p<0.001).[68] Icatibant also reduced the median time to almost complete symptom relief compared with placebo (8.0 vs. 36.0 hours; p=0.012). Researchers stated that patients treated with icatibant reported significantly faster initial symptom improvement compared with placebo (0.8 vs. 3.5 hours; p<0.001). Researchers also reported that the icatibant group (41%) developed fewer adverse events than the placebo group (51%). Five patients treated with icatibant reported treatment-related adverse events that included diarrhea, nausea, dyspepsia, headache, and injection site erythema; and no patient treated with icatibant experienced a serious adverse event.[68] The most common adverse events associated with icatibant's use include (in decreasing order of frequency) injection site reactions, pyrexia, increased transaminase levels, and dizziness.[65] Patients with HAE attacks affecting the larynx are advised to seek medical attention after self-administration of icatibant.[65]

In August 2011, FDA approved icatibant for treating type I or type II acute HAE.[69] BioRx (Cincinnati, OH) entered a limited agreement with Shire to distribute icatibant in the United States.[70]

According to one online pharmacy, the retail cost of one 30-mg dose of icatibant is about $8,400.[71] The retail cost of one 30-mg dose of ecallantide (Kalbitor®), a recently approved competitor to icatibant, was listed at about $9,500.[71] Shire created two programs, Quick Start and

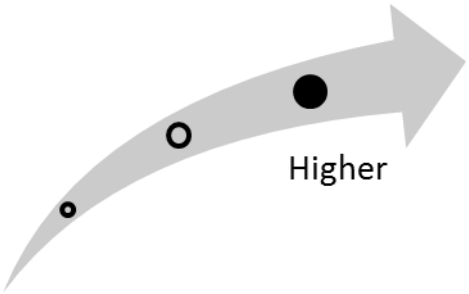
extended OnePath Access, to offer product-related services and support to patients. After a health care provider prescribes the drug, patients can enroll to be eligible to receive two syringes of the drug at no cost.[69]

Our searches of 11 representative, private, third-party payers that provide online coverage policies (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found that 10 payers list coverage determinations for icatibant for treating HAE.[72-81] Generally, payers cover icatibant for patients with type I and II HAE. The drug may have tier 3 or 4 formulary status and third-party payers frequently require preauthorization and prescription by a specialist and enforce quantity limits.[72-81]

Clinical Pathway at Point of This Intervention

Three new drugs have been approved in the United States for treating HAE, in addition to icatibant. Two of the three are given intravenously by a medical professional: Cinryze® and Berinert®, plasma-derived C1INH concentrates purified from human plasma for short-term prophylaxis and acute HAE attacks. The third is given by a medical professional by subcutaneous injection for acute HAE attacks: ecallantide (Kalbitor®), a plasma kallikrein inhibitor.[63] Icatibant can be self administered and has a novel mechanism for HAE treatment to reduce inflammation during acute HAE.

Figure 4. Overall high-impact potential: icatibant (Firazyr) for treatment of acute hereditary angioedema



Overall, experts commenting on this intervention saw icatibant as having significant potential to shorten the duration of symptoms and improve clinical outcomes in the small number of patients who experience HAE, a condition that quickly can become life threatening when it occurs. They noted that although other new treatments have just become available for HAE, icatibant has a different mechanism of action and could be self administered on an outpatient basis, potentially minimizing hospitalizations and the role emergency personnel in managing HAE in a subset of patients. Thus, experts saw the overall impact as high. Based on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered comments on this intervention.[82-88] Overall, experts agreed that although treatment options are available for HAE, acute, unpredictable, life-threatening HAE attacks create a strong unmet need for effective, self-administered treatment.

All experts offering comments agreed that the theory behind the mechanism of icatibant action is sound and that the available data from clinical trials showed promising results that icatibant

appeared efficacious in relieving HAE symptoms within a relatively short time. The combination of rapid relief of symptoms and self administration is expected to improve health outcomes, and reduce emergency department visits and hospitalizations because of HAE.

Overall the experts stated the high price of icatibant could add to health care disparities, suspecting that only patients with third-party coverage would have access to the drug. However one expert representing a research perspective stated that self administration could increase access to treatment for patients who do not live in close proximity to a hospital. Self-administered icatibant is expected to disrupt health care infrastructure and patient management by changing care to the home setting, reducing demands on emergency departments and personnel. However, the rarity of HAE is expected to attenuate these impacts. Patients and clinicians are expected to readily accept the simple and effective home administration of icatibant. But one expert representing a clinical perspective stated that a barrier to acceptance for some clinicians could arise from concern that some patients may not follow up with their physician after an HAE attack, because the drug could provide close to total symptom relief. Failure to follow up could negatively affect health outcomes. Although the cost per dose of icatibant is perceived to be high by most experts, icatibant was still thought to be cost saving because of the high cost of hospitalization. Additionally, the rarity of HAE and the unpredictability of attacks could also result in some pharmacies losing money from stocking icatibant that expires unused.

Overall, experts viewed icatibant as having significant potential to shorten the duration of symptoms and improve clinical outcomes in the small number of patients affected by HAE. Icatibant is the first and only approved self-administered treatment option for HAE, and one expert stated that studies should be conducted to compare icatibant with intravenous options so clinicians can fully understand the risk-benefit profile of the drug.

Hematologic Disorder Intervention

OBI-1 for Treatment of Acquired Hemophilia A

Acquired hemophilia is a rare disease occurring mostly in middle-aged individuals and rarely in children. An estimated 20,000–25,000 individuals in the United States have some type of hemophilia.[89,90] Acquired hemophilia is rare and affects approximately 1–4 individuals per 1 million population.[90] Current therapies, specifically human factor VIIa (NovoSeven®) and factor VII inhibitor bypassing activity (FEIBA™), work by bypassing the coagulation cascade, producing extremely higher-than-normal levels of factor VIIa to induce coagulation.[91] However, novel therapies are needed to more effectively address the underlying pathogenesis of acquired hemophilia, in which autoantibodies produced against the body's coagulation factors result in excessive bleeding episodes. OBI-1 (Inspiration Biopharmaceuticals, Inc., Cambridge, MA, and Ipsen, Paris, France) therapy is purported to address the unmet need of patients receiving a diagnosis of acquired hemophilia A.

OBI-1 is an intravenous, recombinant, porcine factor VIII product that serves as factor VIII replacement therapy by activating the natural coagulation cascade.[91] In acquired hemophilia, the production of autoantibodies in adult life inactivates factor VIII, causing hemophilia type A. This therapy purportedly has low cross reactivity with autoantibodies against factor VIII, significantly reducing immunogenicity of the antigen to recombinant porcine factor VIII. In one study, OBI-1 was evaluated in patients with congenital hemophilia A. Results from this study demonstrated that OBI-1 has the capacity to stop the bleeding in all study participants, which paved the way for investigation of its efficacy for acquired hemophilia A.[92] In an ongoing phase II/III trial, OBI-1 is being given by intravenous infusion over a period of 2–3 hours in treating patients who have acquired hemophilia A.

In July 2011, Inspiration Biopharmaceuticals announced results from its pivotal trial in the OBI-1 Accur8 clinical trial program. OBI-1 treatment was given to three patients with acquired hemophilia who had experienced severe bleeds uncontrolled by other therapeutic agents. Bleeding stopped in all three patients. A larger phase III trial that will enroll 28 patients started in 2011.[93,94] Inspiration Biopharmaceuticals filed for chapter 11 bankruptcy protection from creditors in October 2012, and Ipsen acquired worldwide development rights to OBI-1.[95] Inspiration Biopharmaceuticals stated in a press release that, "Inspiration is seeking a strategic buyer through a formal sale process. Inspiration and Ipsen have jointly chosen an investment banker to lead the sale process, and Inspiration is negotiating the terms of the engagement. Ipsen has agreed to provide Debtor-in-Possession (DIP) financing to Inspiration to fund Inspiration's operations through the sale process. Ipsen will also include their commercialization rights to Inspiration's products, received from Inspiration in a transaction completed on August 21, 2012, and its OBI-1 manufacturing facility based in Milford MA as part of the assets offered for sale."[96]

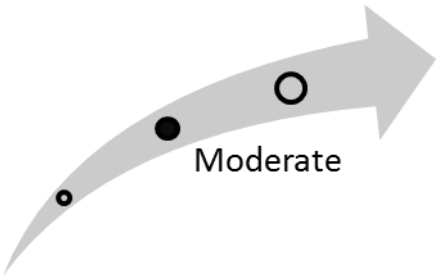
FDA granted OBI-1 orphan drug status in March 2004. The European Commission also granted orphan drug status.[92]

Clinical Pathway at Point of This Intervention

Patients with acquired hemophilia A present a pattern of bleeding (extensive purpura) that is different from common congenital forms of the disease (bleeding into joints).[90] Primary care providers may be the first to encounter the patient, who is then referred for a hematology consultation, ideally at a comprehensive hemophilia treatment center. These centers provide a multidisciplinary approach that includes a team consisting of hematologists, nurses, social workers, physical therapists, and other health care providers.[89] According to the U.S. Centers for Disease Control and Prevention, treatment involves replacing the missing clotting factor through plasma-

derived concentrate or genetically engineered recombinant factors (i.e., not from plasma) of the missing factor, cryoprecipitate for acute bleeding episodes, or other medications intended to induce clotting, such as DDAVP (desmopressin acetate) and Amicar® (epsilon aminocaproic acid).[89] For acquired hemophilia, treatment also targets production of the antibody inhibitors.[90] OBI-1 is proposed as a treatment for acute bleeding episodes in patients with acquired hemophilia A who have developed inhibitors to human factor VIII.

Figure 5. Overall high-impact potential: OBI-1 for treatment of acquired hemophilia A



Overall, experts expressed optimism about OBI-1's potential to address the need for effective first-line treatment for acquired hemophilia, highlighting its sound mechanism of action. Experts thought that it has the potential to change the treatment model for this condition. However, experts also opined that further studies evaluating efficacy and safety are needed to confirm its promise. Experts remained divided on per-patient costs with OBI-1 therapy, but thought clinicians and patients would be very accepting of this therapy because of the lack of other effective treatments, marking its potential for high impact. Based on this input, our overall assessment is that this intervention is in the moderate end of the high-potential-impact range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this intervention.[97-102] Experts agreed that an unmet need exists for more effective therapy aimed at stimulating the natural coagulation cascade and counteracting inhibition of clotting factors by autoantibodies. One expert with a clinical perspective opined that recombinant porcine factor VIII therapy could initiate the normally occurring coagulation cascade, therefore providing a more effective and beneficial therapy option.

Experts agreed that the underlying mechanism of action of OBI-1 therapy is quite sound. One expert with a clinical background stated, "OBI-1 is a unique alternative to treating inhibitors with bypassing agents, such as factor VII products. OBI-1 is safe and effective for the treatment of serious bleeding episodes in individuals with acquired hemophilia A."[97] Another expert with a clinical perspective opined that OBI-1 "offers the biologic activity in replacement form of human factor VIII without the immunogenicity of the human factor."[102] Another expert indicated that the underlying mechanism for OBI-1 therapy seems sound and appears to offer a low risk of adverse events to this patient population. Experts were cautiously optimistic about OBI-1's potential to improve health outcomes, stating that additional studies are needed to confirm efficacy.

Experts' comments were generally mixed regarding whether OBI-1 therapy has the potential to inform current understanding of acquired hemophilia. One expert with a clinical perspective indicated that increased understanding of this therapy's mechanism of action "could lead to other therapies using a similar evasive approach."[102] Most experts believe that this therapy has potential to offer patients an effective therapy option within the current treatment model. These experts claimed that OBI-1 therapy incorporation into the current care model may also offer a new

perspective on future treatment modalities for treating acquired hemophilia. However, several experts believe that the current care system would not be disrupted by incorporation of OBI-1 therapy and that it might be used as an adjunctive therapy.

Experts were divided when considering the effects of per-patient costs of care with OBI-1. One expert with a clinical perspective opined that cost savings or increase will be negligible because acquired hemophilia is an orphan disease. Experts generally agreed that patient acceptance for OBI-1 therapy would be high and that if proven efficacious, this recombinant porcine coagulation factor VIII product has the potential for high impact.

Pain Intervention

Orally Inhaled Dihydroergotamine (Levadex) Treatment for Migraine Headache

Migraine headache is one of the most common chronic pain disorders, affecting an estimated 28 million people each year in the United States.[103] Many patients are not satisfied with their current migraine treatment because of inconsistent response to the medication, high migraine recurrence rates after treatment, and/or slow onset of action of the medication.[104] Therefore, new treatments for migraine headache are highly desired.

One commonly employed migraine treatment is the ergot alkaloid dihydroergotamine mesylate (DHE).[103] Although DHE's exact mechanism of action is unclear, it is proposed to act as an agonist of various 5-hydroxytryptamine 1 (5-HT1 [serotonin]) receptors and could mitigate migraine symptoms by causing meningeal vasoconstriction and trigeminal inhibition of proinflammatory neuropeptide release.[105] DHE is available as an injectable solution and as a nasal spray.[105]

Levadex® (MAP-004, MAP Pharmaceuticals, Inc., Mountain View, CA) is a novel, orally inhaled formulation of DHE that is delivered by its developer's proprietary Tempo™ breath-activated metered dose inhaler.[106,107] Compared with currently available, injectable DHE, Levadex is purported to be more convenient and faster acting with fewer side effects for patients who are known to respond to DHE.[108] Preliminary data suggest that patients treated with Levadex might not experience nausea and vomiting as often as patients treated with intravenous DHE.[108] The developer claims that, compared with the currently available nasal-spray DHE formulation, inhaled Levadex would avoid the nasal irritation and inconsistent absorption often observed with nasal-spray delivery.[104]

In April 2011, Aurora and colleagues published results from a randomized, double-blind, phase III trial comparing Levadex with placebo for treating 903 patients who experience migraines.[109] Of the 903 patients, 792 had a qualifying migraine during the trial (395 patients in the Levadex arm and 397 patients in the placebo arm), and researchers reported that Levadex met its primary endpoints of superiority to placebo in the percentage of patients who reported pain relief (58.7% vs. 34.5%; $p<0.0001$), freedom from heightened auditory sensitivity (52.9% vs. 33.8%; $p<0.0001$), freedom from heightened light sensitivity (46.6% vs. 27.2%; $p<0.0001$), and no nausea (67.1% vs. 58.7%; $p=0.0210$).[109]

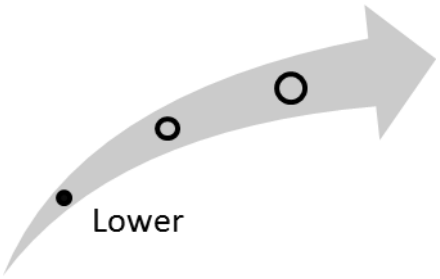
In August 2011, MAP Pharmaceuticals filed an NDA for Levadex for treating migraine headache and FDA accepted the submission for review. In March 2012, FDA issued a complete response letter requesting that the manufacturer address issues relating to chemistry, manufacturing, controls, and a facility inspection at a third-party manufacturer.[110] FDA was also unable to complete a review of inhaler usability information it had requested late in the review cycle. FDA did not cite any clinical safety or efficacy issues or request any additional clinical studies for approval. The manufacturer planned to meet with FDA to address issues raised in the complete response letter.[110] After June 2012 meetings with FDA to identify a way forward, the manufacturer resubmitted the NDA for Levadex in October 2012 to FDA.[111] The company issued a press release on November 21, 2012 stating that FDA had classified the resubmission as complete.

Clinical Pathway at Point of This Intervention

Patients with mild to moderate migraine headaches are typically treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Patients experiencing more severe symptoms and those who do not respond to NSAIDs may be treated with migraine-specific drugs such as triptans or DHE. Several existing formulations are available for triptans and DHE, and patients' use of one treatment

over another is based mainly on delivery method preference and response to treatment. Levadex would represent another delivery option for DHE treatment of acute migraine headache.

Figure 6. Overall high-impact potential: orally inhaled dihydroergotamine (Levadex) treatment for migraine headache



Overall, experts providing comments on this topic believe that a significant unmet need exists for an improved formulation of DHE that could allow fast, easy, and effective self administration. Experts generally agreed that Levadex has potential to significantly improve pain outcomes more than that achieved by current DHE formulations. However, several experts were concerned about potential side effects and opined that potential clinical acceptance may be affected by the overall safety of this intervention. Based on this input, our overall assessment is that this intervention is in the lower end of the high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered comments on this intervention.[112-118] The experts were generally optimistic about the significance of an orally inhaled DHE formulation to address the unmet need of better migraine treatments, noting that Levadex provides an alternative therapy option for patients who are unresponsive to NSAIDs. However, one expert with a health systems perspective deemed that the benefit was incremental when comparing oral to nasal inhalation. One expert with a clinical background expressed the opinion that an orally inhaled delivery method has the potential for more consistent dosing than the nasal spray formulation and offers more convenience than injected formulations. One expert with a research perspective noted that, given the delivery method of Levadex, the care setting would shift to a home setting.

Several experts had concerns regarding the delivery method and suggested that patient training would be needed to ensure accurate dosing. One expert with a clinical perspective opined, "DHE is available as a nasal spray but efficacy is unpredictable due to the poor delivery system."[117] However, one expert with a research perspective stated that the benefit of Levadex's route of administration over nasal administration was minimal at best. Several experts noted contraindications associated with DHE and suggested that care providers need to be educated if they are not comfortable prescribing DHE. One expert from a clinical perspective commented, "There are some concerns with the use of DHE but it should be accepted. Ergots can cause cardiac, cerebral, or peripheral ischemia in some high risk patients." [113] Experts generally agreed that training would be needed for patients and clinicians alike on using the Levadex inhaler to ensure proper dosing.

As a formulation change to an existing treatment, Levadex would not cause significant changes to migraine treatment models, health care staffing, or health care infrastructure, experts believe. However, multiple experts noted that Levadex has the potential to reduce visits to the emergency department, where intravenous infusion for migraine treatment would likely be administered. The

change from emergency department intravenous infusion to at-home self administration figured prominently experts' estimates of Levadex's impact on health care costs. One clinical expert opined, "The cost of the inhaler could have a significant impact if it lowers ER visits for migraine, inpatient admissions, and provides an alternative to opioids or barbiturates (which frequently lead to abuse or addiction)."[117]

Sensory Disorder Intervention

Recombinant Human Ocriplasmin (Jetrea) Injection for Treatment of Focal Vitreomacular Adhesion

Before the recent FDA approval of ocriplasmin (formerly microplasmin), treatment options for symptomatic vitreomacular adhesion were limited to invasive vitreoretinal surgical procedures. However, the efficacy of these invasive procedures is limited by the potential for incomplete vitreoretinal separation and/or removal, surgical complications (e.g., development of cataracts), and high costs.[119] Therefore, clinicians have significant interest in nonsurgical methods that could replace or complement surgical treatments for vitreoretinal conditions such as vitreomacular adhesion.[120] Recently approved by FDA, ocriplasmin (Jetrea®, ThromboGenics NV, Heverlee, Belgium) is an enzymatic vitreolysis agent that is used as an intravitreal injection for treating symptomatic vitreomacular adhesion.[121]

Focal vitreomacular adhesions are characterized by a vitreous gel with an abnormally strong bond to the retina; the adhesions affect the development and progression of numerous back-of-the-eye conditions and have been associated with a poor prognosis in diabetic retinopathy and age-related macular degeneration.[122,123] Retina specialists are greatly interested in finding an intravitreously injected agent that can both induce liquefaction of the vitreous and disrupt adhesion between the vitreous and the retina, leading to completion of posterior vitreous detachment.[119] Potential targets for anti-adhesive interventions are components of the extracellular matrix, such as laminin, fibronectin, chondroitin, and integrins, that are thought to act as a "molecular glue" between the vitreous and the retina.[124]

Ocriplasmin is a truncated form of plasmin produced using recombinant methods in a yeast (*Pichia pastoris*) expression system.[125] Recombinant ocriplasmin retains the catalytic characteristics of human plasmin and is purported to have several advantages as a therapeutic agent, including sterility because of the recombinant techniques used to generate it; smaller size than plasmin, potentially allowing greater penetration of epiretinal tissues; and greater stability than plasmin.[119,124] Phase III clinical trials used an intravitreal injection of 125 mcg.[126] Intravitreal injections require a local anesthetic (eye drops) to minimize discomfort to the patient and an antiseptic solution to prevent contamination when injecting the solution into the eye.[127]

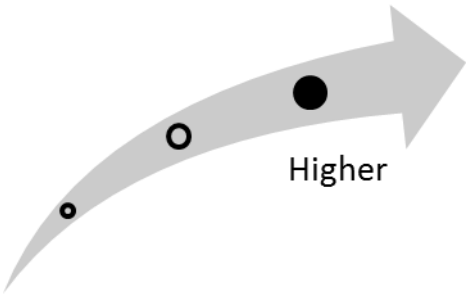
In 2010, ThromboGenics reported pooled results from the TG-MV-006 and TG-MV-007 phase III trials conducted on 652 patients at 48 centers in Europe and the United States.[128] Both trials met the primary endpoints with 26.4% of the 465 ocriplasmin-treated patients achieving resolution of their vitreomacular adhesions at 28 days, compared with 10.2% of 182 patients who received a placebo injection (p=0.000002). In patients without epiretinal membrane, 37.4% of 270 patients given ocriplasmin injections achieved nonsurgical resolution of their vitreomacular adhesions at 28 days compared with 14.3% of 119 patients treated with placebo (p=0.000003). The pooled results, stated the investigators, confirmed that ocriplasmin was generally safe and well tolerated. The investigators stated that there was no evidence of an increased risk of retinal tear or detachment.[128]

The company submitted a biologics license application (BLA) to FDA in December 2011.[129] However, in February 2012, ThromboGenics announced that it had withdrawn the original BLA after FDA stated that it would grant ocriplasmin priority review status, and the company resubmitted the BLA to meet the priority review requirements.[130] In October 2012, FDA approved ocriplasmin for treating symptomatic vitreomacular adhesion.[131] The labeled recommended dose is 0.125 mg (0.1mL) of the diluted solution administered by intravitreal injection to the affected eye once as a single injection.[132]

Clinical Pathway at Point of This Intervention

Patients with vitreomacular adhesion may present with symptoms of decreased or distorted central vision. An optical coherence tomography test may help clinicians arrive at a diagnosis of vitreomacular adhesion. Patients in whom asymptomatic or mildly symptomatic vitreomacular adhesion is diagnosed typically undergo watchful waiting, and some cases of vitreomacular adhesion may spontaneously resolve. Patients with significant visual impairment caused by vitreomacular adhesion typically undergo vitrectomy (i.e., removal of the vitreous).[133] Intravitreal injection with ocriplasmin may provide a nonsurgical method to resolve vitreomacular adhesion.[121]

Figure 7. Overall high-impact potential: recombinant human ocriplasmin (Jetrea) injection for treatment of focal vitreomacular adhesion



Experts commenting on this intervention thought that, for patients most affected by focal vitreomacular adhesion, recombinant ocriplasmin injection therapy could offer an alternative for a condition in which invasive surgical intervention is the primary standard of treatment. Some experts believe that ocriplasmin injection could serve as first-line therapy for patients and thought that the treatment could eliminate the need for the surgical intervention. A potential shift in care setting and management could occur, transitioning to more outpatient care with care potentially being provided by a retinal specialist. The majority of experts thought that an alternative therapy to surgical intervention would decrease treatment costs. However, one expert noted that the overall costs would increase for patients in whom the condition fails to resolve, so they still need surgery. Based on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, offered comments on this intervention.[134-139] The experts agreed that treatment options for focal vitreomacular adhesion are primarily limited to surgery, and effective and safe noninvasive treatment is necessary for this population. One expert with a research perspective expressed, "other treatments do exist (vitrectomy); however, they carry significant risks."[139] However, the same expert noted the limited amount of published research and questioned the efficacy of this intervention.

All experts agreed that the underlying mechanism for recombinant ocriplasmin injection appears sound and promising, with several experts citing efficacy in clinical studies as quantitative proof of the intervention's concept. Concerning ocriplasmin injection's impact on patient health outcomes, experts agreed that the intervention has potential to eliminate surgical intervention and reduce associated adverse events in this disease population. An expert with a research perspective indicated that the elimination of surgical intervention would not only improve patient health outcomes, but also quality of life.[137] However, one expert with a research perspective would like to see more data

to determine to what degree this intervention prevents a decline in vision and improves the patients' quality of life.[139]

Experts generally agreed on the intervention's potential to disrupt the current care model for this patient population. All experts believe that integration of ocriplasmin injection therapy would affect the current intervention model for patients with focal vitreomacular adhesion. One clinical expert opined that the intervention, "can be performed in the office and avoid surgery at the hospital."[134] Regarding potential shift in patient management, most experts believe recombinant human ocriplasmin injection may reduce or eliminate the need for vitreomacular surgery. One expert with a research perspective noted, "This method of treatment should significantly alter current methods for managing the condition."[137] But one expert with a health systems perspective believes that there would not be any change to patient management for this disease.

Most experts agreed that per-patient cost would decrease with reduction of surgical interventions for this patient population. However, one expert with a research perspective noted that the overall costs would increase for patients in whom the condition fails to resolve, so they still need surgery.[139] Experts agreed that patients would accept this intervention, because ocriplasmin injection can provide an effective alternative to surgical intervention. Regarding potential acceptance by patients and clinicians, one clinical expert commented, "The safety profile is excellent. There is no down side to considering the medical approach before offering surgery."[138] Overall, experts agreed on the unmet need for nonsurgical therapy option for treating vitreomacular adhesion and that the therapy has potential for high impact.

Spinal Cord Injury Rehabilitation Interventions

Computerized Walking Systems (ReWalk and Ekso) for Patients With Paraplegia From Spinal Cord Injury

Currently, conventional manual and powered wheelchairs are the primary assistive devices to restore some degree of mobility in people with paraplegia. However, these devices do not help users walk or climb stairs. Two reciprocating gait orthosis systems in development, the ReWalk system (Argo Medical Technologies, Ltd., Yokneam Ilit, Israel) and the Ekso system (Ekso Bionics, Richmond, CA), may provide greater mobility and freedom to people with paraplegia from spinal cord injury.

The ReWalk system comprises a set of computer-controlled, motorized leg braces that restore the ability to walk with crutches to patients with paraplegia who retain the ability to use their hands and shoulders to walk with crutches and who have good bone density and cardiovascular health. The wearable support system uses an array of sensors and proprietary computer algorithms to analyze body movements and manipulate the motorized leg braces to help users maintain proper gait using crutches for walking, climbing stairs, and other movements. The onboard computer, sensor array, and rechargeable batteries that power the wearable exoskeleton are contained in a backpack that users wear in addition to the leg braces. The ReWalk system weighs about 35 lb.[140]

The Ekso (formerly eLegs) system is another powered exoskeleton device for patients with paraplegia or lower-extremity paresis due to neurologic diseases, including spinal cord injuries, multiple sclerosis, amyotrophic lateral sclerosis, or Guillain-Barré syndrome. It incorporates technology similar to that in the ReWalk system. The 45-lb Ekso system is based on the Human Universal Load Carrier, a motorized exoskeleton designed to allow users to carry up to 200 lb continuously for several hours over any terrain that the U.S. military uses. The manufacturer carried out clinical testing of the Ekso system in 12 U.S. rehabilitation hospitals in 2011 and early 2012.[141] The manufacturer states that transfer to and from a patient's wheelchair and this powered exoskeleton device takes less than 5 minutes and that the user requires little to no assistance.[142] The company estimates the battery life for this device to be 3 hours.[142]

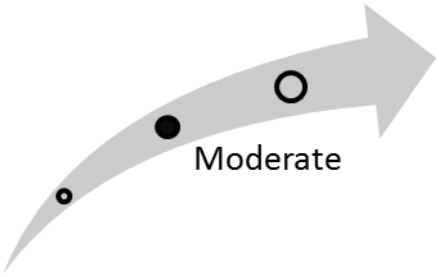
FDA classifies the ReWalk reciprocating gait orthosis as powered exercise equipment (product code BXB) used for medical purposes (e.g., physical therapy), thus making the technology exempt from 510(k) premarket notification or premarketing approval application procedures.[143] Such products require only FDA device registration and listing. As of November 2011, the ReWalk-I system was listed by FDA for institutional use only, reportedly costing about $105,000 per system. According to a published report, the company expects to soon register ReWalk-P for personal use for those who qualify upon medical examination and rehabilitation training, costing about $20,000, although this has not been confirmed with the manufacturer.[144] According to the Ekso system's manufacturer, its system became available to the Craig Hospital (Denver, CO) in February 2012, the company's first commercial health care participant, for institutional use.[141] The cost of the Ekso institutional system is about $130,000, with anticipated costs for personalized Ekso exoskeletons to be $50,000–$75,000.[145]

Clinical Pathway at Point of This Intervention

Occupational and physical therapists work with patients after acute treatment of spinal cord injury to evaluate their functional abilities, determine what type of rehabilitation is appropriate, implement specific exercises and routines, and determine the type of assistive devices that could help them become more independent with daily living skills.[146] Currently, conventional manual and powered wheelchairs are the primary assistive devices used to restore mobility to people with paraplegia. The ReWalk and Ekso reciprocating gait orthosis systems would be used to assist

patients with paraplegia to stand and move, improving their quality of life by increasing their mobility and independence.

Figure 8. Overall high-impact potential: computerized walking systems (ReWalk and Ekso) for patients with paraplegia from spinal cord injury



Experts thought that the high cost and complexity of this technology could limit its introduction and diffusion into the mainstream of rehabilitative services and centers treating patients with paraplegia from spinal cord injury. They expected that staffing models would be affected by the need for clinical and software engineers and technicians to maintain and adjust the equipment. Also, they thought that the equipment would likely be appropriate only for patients with robust health. Experts indicated that the intended population has very limited treatment options, and they agree on the vast potential benefit of computerized walking systems. Based on this input, our overall assessment is that this intervention is in the moderate end of the high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, commented on this intervention. [147-152] Experts generally agreed that a major benefit of this intervention would be psychological, allowing patients to have improved self image, reduced depression, and increased ability to participate in social interactions. Aside from psychological benefits, several experts opined that this intervention could improve patient health outcomes with respects to pressure ulcer incidence. Regarding pressure ulcers in paraplegic patients, one expert with a clinical perspective opined, "These decubiti can be very detrimental and have significant morbidities. These skin issues can get infected and often require surgical intervention."[148]

Cost was a limiting factor mentioned by the experts in terms of access and diffusion, especially to populations affected by health disparities and by limited access to rehabilitative services. The estimated device cost ranges between $105,000 and $130,000 for institutional use and between $20,000 and $75,000 for personal use, plus the cost of software programing and adjustments. One expert with a research perspective commented, "[C]ost will be substantial and this will definitely limit diffusion and adoption."[147]

Several experts with research perspectives agreed that this type of device could greatly disrupt the current healthcare delivery infrastructure. One expert noted, "Physical therapists, medical professionals, and biomedical engineers would need to be trained on the risks, control, and maintenance of this device."[153]

Experts generally agreed that this intervention has significant potential to provide patients with improved overall quality of life, especially considering the lack of available treatment options. However, one expert with a research perspective commented that patients would prefer the use of a wheelchair, even after trying a computerized walking system. Experts from both research and clinical perspectives agreed that this technology had the potential to spur further technological innovations for treating this patient population.

Intraoral Tongue-Drive Computerized System to Maneuver Electrically-Powered Wheelchairs

Although conventional manual and powered-assisted devices exist that attempt to improve quality of life for individuals with paraplegia, efficacy and safety issues remain a primary concern. Specifically, regarding neuroassistive technology for this patient population, surgical invasiveness and risk of adverse events remain factors that may decrease patient acceptance and overall quality of life. Using a magnetic, pierced-tongue aid system, a tongue-operated assistive neurotechnology for managing spinal cord paralysis, would represent a novel device that might enhance patient mobility and allow patients to perform more daily tasks in a safer and more effective manner with less-invasive technology.

The Tongue Drive System (TDS, Georgia Institute of Technology, Atlanta) is a computerized, tongue-operated, assistive neurotechnology. It consists of a lentil-sized magnetic tracer/stud that is embedded in a dental retainer worn in the mouth with the tracer affixed to the tongue, most commonly by piercing.[154,155] The tracer/stud creates a magnetic field around the pierced glossal area, and magnetic sensors located on a wireless headset and headphones communicate with a wheelchair. Because the tongue is a durable muscle that does not tire easily and is generally spared in spinal cord injuries and neuromuscular diseases, it was designated an ideal target for this neuroassistive technology.[156] The change in magnetic field (prompted by tongue movement) in the mouth is detected by the magnetic sensors on the headset, transmitting information wirelessly to a smartphone carried by the patient. The smartphone can then transmit information to a wheelchair or computer, commanding these devices to perform tasks such as wheelchair movement or daily computer tasks (e.g., email).[156] This system can be recharged via USB after 2 days of continuous use. A standby mechanism allows patients to perform daily tasks, such as eating, sleeping, and conversing, without unnecessary use of the TDS.[156] Patients must undergo computer training for the computer program to appropriately interpret and calibrate tongue movement, allowing proper control of the wheelchair and computer device.[154]

In 2009, Ghovanloo and colleagues published results from a trial of five patients with tetraplegia to determine the usability of the TDS for patients with spinal cord injury.[157] "Each subject completed the course at least twice using each strategy while the researchers recorded the navigation time and number of collisions. Using discrete control, the average speed for the five subjects was 5.2 meters per minute and the average number of collisions was 1.8. Using continuous control, the average speed was 7.7 meters per minute and the average number of collisions was 2.5."[157] A trial is ongoing at two rehabilitation centers, one in Atlanta, GA, and the other in Chicago, IL.[155] The National Science Foundation, the Christopher & Dana Reeve Foundation, and the National Institute of Biomedical Imaging and Bioengineering at the National Institutes of Health are helping to fund development of the system.

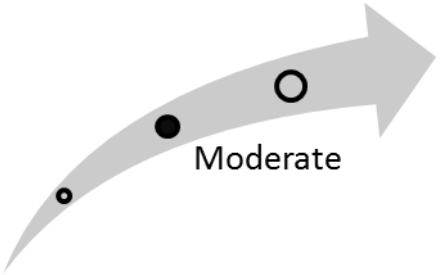
The TDS has not yet been approved by FDA. No cost information about the device was identified.

Clinical Pathway at Point of This Intervention

After patients receive acute treatment for spinal cord injuries, they work with occupational therapists who evaluate their functional abilities and determine what type of rehabilitation is appropriate and who work with patients to implement specific exercises and routines and determine what type of assistive devices could help patients become more independent with daily living skills.[146] Conventional manual and powered wheelchairs currently used have considerable

limitations in restoring mobility and improving quality of life for patients who have spinal cord injuries. The magnetic pierced-tongue aid would provide patients with the ability to perform tasks, such as wheelchair movement or daily computer and phone tasks, through synergistic communication between a tongue-mounted magnetic tracer, magnetic sensors, smartphones, computers, and wheelchairs.

Figure 9. Overall high-impact potential: intraoral tongue-drive computerized system to maneuver electrically-powered wheelchairs



Experts commenting on this intervention thought that the intraoral magnetic tongue-directed aid could be a viable alternative to existing technologies. Although some experts thought the unmet need was not extremely significant, other experts who commented have worked directly with patients using assistive devices to control powered wheelchairs and believe this intervention could significantly improve patient health outcomes and quality of life, allowing patients to perform daily activities in a quicker and less exhausting manner. Several experts thought safety concerns could be a barrier to clinician acceptance, because device malfunction might harm the user. Overall, this device's perceived complex nature, the existence of comparators, and limited safety and efficacy data thus far have made some experts question device's true impact potential. However, other experts believe this device has the ability to significantly improve patient mobility and quality of life, compared with standard mobility devices. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Nine experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this intervention.[158-166] Generally, experts opined that a significant need exists in introducing new assistive technology aimed at restoring mobility in patients with spinal cord injury. Several experts reported the magnetic tongue-directed neuroassistive device could become a viable alternative technology to conventional manual and powered devices for this patient population. One research expert mentioned the potential efficiency of this device in terms of control and communication, stating, "I've worked with people using puff-straws, joysticks, and head-paddles, but this looks appropriate for patients with a much higher degree of impairment than [those who use] head paddles and joysticks. Also, unlike air puff, this system is more sensitive and can speed up communication and control tasks. Air puff systems take forever to get anything done and I've seen users get frustrated."[158] Another research expert believes the TDS has the ability to replace currently available assistive devices, stating, "it is relatively discreet, quick to respond to commands, unobstructive to one's senses, and can be used for long periods of time without excessive strain."[159] However, several experts thought this device might not significantly affect this patient population, suggesting the availability of numerous alternatives believed to effectively restore mobility, including sip-and-puff, chin-control, head-control, and speech-control assistive devices.

Experts were divided on this intervention's potential to improve patient health outcomes. Experts expressed concerns over limited efficacy and safety studies available for this device. A research expert stated that although this device could improve mobility and increase patient quality of life, concerns over potential device malfunction and collision remain. Several experts affirmed the need for comparative studies with currently available assistive devices to determine whether a clear benefit to using the TDS exists. One clinical expert expressed skepticism over its ability to improve health outcomes, because this device does not directly affect a patient's health. However, one health systems expert opined that the technology seems usable based on available studies and would allow patients to communicate at "normal or near-normal" speed. It seems likely to provide significant mobility improvement over conventional assistive devices, allowing for more patient participation in daily social activities.[158] Another expert stated this intervention could allow patients to perform daily activities with a greater degree of ease over available comparators. This expert states "the key here is the technologies involved to capture, interpret, and transmit intent - and then further, the devices, systems, and equipment that carry out such intent. I believe use of smart phones, in several of these roles, is a good start. Working towards systems that are easy to replace and control is a must..."[164]

Experts generally agreed this neuroassistive device would not significantly affect health disparities, although one clinical expert opined that the anticipated cost of this device could increase health disparities. Most experts shared opinions that this device would not significantly disrupt the current health care delivery infrastructure or patient management, stating that the system currently in place is readily equipped for this device's implementation and adoption. Several experts conceded adoption of this device might require increased hiring of rehabilitation specialists, computer specialists, and biomedical hardware specialists to train patients and ensure proper functioning of this device. One expert believes that the anticipated increase in specialists for this device in combination with the device's potential complexities may increase time in patient management.

Experts generally agreed that the TDS's potential acceptance by both clinicians and patients would be high. Most experts generally agreed that, provided this device proves safe and effective, it would be easily accepted by clinicians and physical therapists. Three of these experts believe the potential of this device to improve patient dependence would increase patient acceptance. One research expert stated that the device would pose minimal health risks to this patient population while increasing patients' accessibility and communication with society, significantly improving patient outcomes. In terms of patient acceptance, a health systems expert questioned, "How does it affect speech? Does this offend culturally? Religiously? Infection?"[164] Negative perceptions regarding the required tongue piercing for this device seems to be a predominating issue for adoption by elderly patients, according to several experts. One research expert opined that elderly patients may have more reservations than a younger patient population, stating "the elderly patients had already been trained to use other assistive devices and did not want theirs to be replaced."[159]

Overall, experts believe this novel neuroassistive device has potential to address an unmet need of this patient population, as long as further studies evaluate the technology's efficacy and safety and provide evidence of benefit. A research expert summarized the opinions of those experts, believing in this device's ability for high impact, stating the TDS "could be a cost-effective way to help improve the quality of life, mobility, and degree of interaction with electronic devices for patients with high-level spinal cord injuries with limited effects on current healthcare infrastructure."[159]

References

1. Dorne H, Zaidat OO, Fiorella D, et al. Chronic cerebrospinal venous insufficiency and the doubtful promise of an endovascular treatment for multiple sclerosis. J Neurointerv Surg 2010 Dec;2(4):309-11.
2. Rabasseda X. Highlights from the 25th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). Drugs Today 2010;46(1):49-67.
3. Sorbera LA, Dulsat C, Rosa E. Therapeutic targets for multiple sclerosis. Drugs Future 2009;34(5):405-17.
4. Dangond F. Multiple sclerosis. [internet]. New York (NY): WebMD, LLC; 2010 Nov 1 [accessed 2011 Feb 7]. [7 p]. Available: http://www.medicinenet.com/multiple_sclerosis/article.htm.
5. Novartis gains FDA approval for Gilenya, a novel first-line multiple sclerosis treatment shown to significantly reduce relapses and delay disability progression. [internet]. East Hanover (NJ): Novartis; 2010 Sep 22 [accessed 2011 May 2]. [5 p]. Available: http://www.novartis.com/newsroom/media-releases/en/2010/1445917.shtml.
6. How relapsing-remitting MS (RRMS) is diagnosed. [internet]. New York (NY): National Multiple Sclerosis Society [accessed 2011 Mar 11]. [2 p]. Available: http://www.nationalmssociety.org/about-multiple-sclerosis/relapsing-ms/relapsing-remitting-ms-rrms/how-rrms-is-diagnosed/index.aspx.
7. Gilenya (fingolimod) capsules prescribing information. East Hanover (NJ): Novartis Pharmaceuticals Corporation; 2011 Jul. 21 p. Also available: http://www.pharma.us.novartis.com/product/pi/pdf/gilenya.pdf.
8. MS drug under investigation after 11 deaths. In: Drug Discovery & Development [internet]. London (UK): Advantage Business Media; 2011 Jan 20 [accessed 2012 Jan 31]. [2 p]. Available: http://www.dddmag.com/news-MS-Drug-Under-Investigation-After-11-Deaths-12012.aspx.
9. Neuroprotective effects of dimethyl fumarate and monomethyl fumarate on primary cultures of human spinal cord astrocytes after oxidative challenge. [internet]. Gothenburg (Sweden): European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS); 2010 Oct 15 [accessed 2011 May 13]. [1 p]. Available: http://registration.akm.ch/einsicht.php?XNABSTRACT_ID=116907&XNSPRACHE_ID=2&XNKONGRESS_ID=126&XNMASKEN_ID=900.
10. Scannevin RH, Chollate S, Shackett M, et al. Neuroprotective effects of BG-12 and other fumarates on primary cultures of neurons and astrocytes after oxidative challenge. In: 63rd Annual Meeting of the American Academy of Neurology; 2011 Apr 9-16; Honolulu (HI). 2011 Apr 13.
11. BG-12. Drugs Future 2010;35(2):93-7. Also available: http://journals.prous.com/journals/servlet/xmlxsl/pk_journals.xml_article_pr?p_JournalId=2&p_RefId=1424268&p_IsPs=N&p_ispdf=N.
12. Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med 2012 Sep 20;367(12):1098-107. PMID: 22992073
13. Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med 2012 Sep 20;367(12):1087-97. PMID: 22992072
14. Biogen Idec's ongoing dedication to people living with MS showcased in data presented at the 63rd annual meeting of the American Academy of Neurology. [internet]. Weston (MA): Biogen Idec; 2011 Apr 11 [accessed 2011 May 3]. [4 p]. Available: http://www.biogenidec.com/PRESS_RELEASE_DETAILS.aspx?ID=5981&ReqId=1549043.
15. Biogen Idec submits application to FDA for approval of oral BG-12 to treat multiple sclerosis. [internet]. Weston (MA): Biogen Idec; 2012 Feb 28 [accessed 2012 May 7]. [2 p]. Available: http://www.biogenidec.com/press_release_details.aspx?ID=5981&ReqId=1666509.
16. US and EU regulatory authorities accept oral BG-12 marketing applications for review. [internet]. Weston (MA): Biogen Idec; 2012 May 9 [accessed 2012 May 17]. [2 p]. Available: http://www.biogenidec.com/press_release_details.aspx?ID=5981&ReqId=1694087.

17. Biogen Idec receives notification of PDUFA date extension. [internet]. Weston (MA): Biogen Idec; 2012 Oct 18 [accessed 2012 Nov 5]. [2 p]. Available: http://www.biogenidec.com/PRESS_RELEASE_DETAILS.aspx?ID=5981&ReqId=1747042.

18. von Schaper E, Kresge N. Novartis's $48,000 pill spurs U.S. price increases for older MS treatments. [internet]. New York (NY): Bloomberg LP; 2011 Mar 21 [accessed 2011 Nov 16]. [5 p]. Available: http://www.bloomberg.com/news/2011-03-21/novartis-s-48-000-pill-spurs-u-s-price-increases-for-ms-drugs.html.

19. Meacham G. (Ph.D., J.P. Morgan Biotech Research). Personal communication. 2012 May 6.

20. FDA approves new multiple sclerosis treatment Aubagio. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2012 Sep 12 [accessed 2012 Sep 25]. [2 p]. Available: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm319277.htm.

21. Expert Commenter 419. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1008 - Dimethyl fumarate (BG-12) for treatment of relapsing-remitting multiple sclerosis. 2012 Jan 24 [review date].

22. Expert Commenter 671. (PRI, Clinical). Horizon Scanning Structured Comment Form. HS1008 - Dimethyl fumarate (BG-12) for treatment of relapsing-remitting multiple sclerosis. 2012 Jan 13 [review date].

23. Expert Commenter 681. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1008 - Dimethyl fumarate (BG-12) for treatment of relapsing-remitting multiple sclerosis. 2012 Jan 24 [review date].

24. Expert Commenter 834. (External, Research/Scientific/Technical). Horizon Scanning Structured Comment Form. HS1008 - Dimethyl fumarate (BG-12) for treatment of relapsing-remitting multiple sclerosis. 2012 Jan 16 [review date].

25. Expert Commenter 400. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS1008 - Dimethyl fumarate (BG-12) for treatment of relapsing-remitting multiple sclerosis. 2012 Feb 17 [review date].

26. Expert Commenter 404. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS1008 - Dimethyl fumarate (BG-12) for treatment of relapsing-remitting multiple sclerosis. 2012 Jan 24 [review date].

27. Expert Commenter 433. (PRI, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS1008 - Dimethyl fumarate (BG-12) for treatment of relapsing-remitting multiple sclerosis. 2012 Feb 7 [review date].

28. Prescribing information: Potiga (ezogabine) tablets. Research Triangle Park (NC): GlaxoSmithKline; 2011 Jun. 27 p. Also available: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022345s000lbl.pdf.

29. Owen RT. Ezogabine: a novel antiepileptic as adjunctive therapy for partial onset seizures. Drugs Today (Barc) 2010 Nov;46(11):815-22. PMID: 21225020

30. French JA, Abou-Khalil BW, Leroy RF, et al. Randomized, double-blind, placebo-controlled trial of ezogabine (retigabine) in partial epilepsy. Neurology 2011 May 3;76(18):1555-63. PMID: 21451152

31. GlaxoSmithKline and Valeant announce US FDA approval of Potiga (ezogabine). [internet]. London (UK): GlaxoSmithKline; 2011 Jun 13 [accessed 2011 Jul 25]. [3 p]. Available: http://us.gsk.com/html/media-news/pressreleases/2011/2011-pressrelease-468781.htm.

32. Potiga. [internet]. Santa Monica (CA): GoodRx, Inc.; Nov 2012 [accessed 2012 Nov 16]. [9 p]. Available: http://www.goodrx.com/potiga.

33. FDA approved labeling text for Potiga (ezogabine) tablets, CV. [internet]. Research Triangle Park (NC): GlaxoSmithKline; 2012 Mar 15 [accessed 2012 Nov 16]. [21 p]. Available: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022345s001lbl.pdf.

34. Aetna, Inc. Pharmacy clinical policy bulletins: Aetna non-Medicare prescription drug plan. Subject: anticonvulsants. [internet]. Hartford (CT): Aetna, Inc.; 2012 Sep 7 [accessed 2012 Aug 17]. [7 p]. Available: http://www.aetna.com/products/rxnonmedicare/data/2012/CNS2012/anticonvulsants_2012.html.

35. MVP Health Care Medicare Part D policy. Prior authorization group: Potiga. Schenectady (NY): MVP Health Care; 1 p. Also available: http://www.mvphealthcare.com/policies/medicare/Potiga.pdf.

36. Independence Blue Cross. Ezogabine (Potiga). Policy #: Rx.01.119. Philadelphia (PA): Independence Blue Cross; 2012 Oct 1. 3 p. Also available: http://www.ibx.com/pdfs/providers/pharmacy_information/pharmacy_policies/ezogabine_potiga.pdf.

37. Pharmacy medical necessity guidelines: Potiga (ezogabine). Document ID#: 2208587. Watertown (MA): Tufts Health Plan; 2012 Jun 12. 3 p. Also available: http://www.tuftshealthplan.com/providers/pdf/pharmacy_criteria/potiga.pdf.

38. MHCP enrolled providers - pharmacies. Fee-for-service PA criteria sheet - Potiga. [internet]. Minnesota Department of Human Services; 2012 Sep 25 [accessed 2012 Nov 16]. [2 p]. Available: http://www.dhs.state.mn.us/main/idcplg?IdcService=GET_DYNAMIC_CONVERSION&RevisionSelectionMethod=LatestReleased&dDocName=dhs16_171764.

39. HealthPartners. Drug formulary update, October 2012. Minneapolis (MN): HealthPartners; 2012 Oct. 4 p. Also available: http://www.healthpartners.com/ucm/groups/public/@hp/@public/documents/documents/cntrb_034265.pdf.

40. Expert Commenter 396. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS642 - Ezogabine (Potiga) for treatment of epilepsy. 2012 Oct 5 [review date].

41. Expert Commenter 794. (External, Clinical). Horizon Scanning Structured Comment Form. HS642 - Ezogabine (Potiga) for treatment of epilepsy. 2012 Sep 10 [review date].

42. Expert Commenter 524. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS642 - Ezogabine (Potiga) for treatment of epilepsy. 2012 Oct 5 [review date].

43. Expert Commenter 82. (External, Clinical). Horizon Scanning Structured Comment Form. HS642 - Ezogabine (Potiga) for treatment of epilepsy. 2012 Sep 10 [review date].

44. Expert Commenter 1015. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS642 - Ezogabine (Potiga) for treatment of epilepsy. 2012 Sep 13 [review date].

45. Expert Commenter 427. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS642 - Ezogabine (Potiga) for treatment of epilepsy. 2012 Oct 5 [review date].

46. Expert Commenter 433. (External, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS642 - Ezogabine (Potiga) for treatment of epilepsy. 2012 Oct 8 [review date].

47. Sponsor summary for Solesta - P100014 for Center for Devices and Radiological Health (CDRH) advisory panel. Edison (NJ): Oceana Therapeutics, Inc.; 2010 Dec 2. 65 p.

48. Graf W, Mellgren A, Matzel KE, et al. Efficacy of dextranomer in stabilised hyaluronic acid for treatment of faecal incontinence: a randomised, sham-controlled trial. Lancet 2011 Mar 19;377(9770):997-1003. PMID: 21420555

49. Oceana Therapeutics announces U.S. launch of Solesta, the only nonsurgical FDA approved treatment for patients who fail conservative therapy for fecal (bowel) incontinence. [internet]. Edison (NJ): Oceana Therapeutics; 2011 Sep 6 [accessed 2011 Sep 12]. [2 p]. Available: http://www.oceanatherapeutics.com/node/86.

50. CIGNA Health Corporation. CIGNA medical coverage policy: injectable bulking agents for urinary conditions and fecal incontinence. Policy number 0206. [internet]. Bloomfield (CT): CIGNA Health Corporation; 2011 Dec 15 [accessed 2012 Nov 16]. [13 p]. Available: http://www.cigna.com.

51. Aetna, Inc. Clinical policy bulletin: fecal incontinence treatments. Number: 0611. [internet]. Hartford (CT): Aetna, Inc.; 2012 Oct 5 [accessed 2012 Nov 16]. [19 p]. Available: http://www.aetna.com/cpb/medical/data/600_699/0611.html.

52. Health Net Associates. National medical policy. Subject: fecal incontinence treatments. Policy number: NMP325. California: Health Net Associates; 2012 Aug. 20 p. Also available: https://www.healthnet.com/static/general/unprotected/pdfs/national/policies/FecalIncontinence.pdf.

53. Blue Cross Blue Shield of Massachusetts. Providerfocus. Boston (MA): Blue Cross Blue Shield of Massachusetts; 2012 Jan. 8 p p. Also available: https://www.bluecrossma.com/staticcontent/newsissues/Provider%20Focus-January%202012-84.pdf.

54. Horizon Blue Cross Blue Shield of New Jersey. Solesta (dextranomer and sodium hyaluronate gel for submucosal injection). Policy number: 137. [internet]. Newark (NJ): Horizon Blue Cross Blue Shield of New Jersey; 2012 Jun 12 [accessed 2012 Nov 16]. [4 p]. Available: https://services3.horizon-bcbsnj.com/hcm/MedPol2.nsf/MedicalPolicies/KKPR-8MJP3P.

55. Mayo Clinic staff. Fecal incontinence. [internet]. Rochester (MN): Mayo Foundation for Medical Education and Research (MFMER); 2010 Aug 14 [accessed 2012 May 25]. [11 p]. Available: http://www.mayoclinic.com/health/fecal-incontinence/ds00477/.

56. Expert Commenter 551. (External, Clinical). Horizon Scanning Structured Comment Form. HS1153 - NASHA Dx (Solesta) for treatment of fecal incontinence. 2012 Jan 17 [review date].

57. Expert Commenter 447. (PRI, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS1153 - NASHA Dx (Solesta) for treatment of fecal incontinence. 2012 Feb 13 [review date].

58. Expert Commenter 421. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1153 - NASHA Dx (Solesta) for treatment of fecal incontinence. 2012 Jan 24 [review date].

59. Expert Commenter 343. (External, Clinical). Horizon Scanning Structured Comment Form. HS1153 - NASHA Dx (Solesta) for treatment of fecal incontinence. 2012 Feb 6 [review date].

60. Expert Commenter 1014. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS1153 - NASHA Dx (Solesta) for treatment of fecal incontinence. 2012 Feb 3 [review date].

61. Expert Commenter 413. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS1153 - NASHA Dx (Solesta) for treatment of fecal incontinence. 2012 Jan 24 [review date].

62. Expert Commenter 427. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1153 - NASHA Dx (Solesta) for treatment of fecal incontinence. 2012 Jan 24 [review date].

63. Gras J. Icatibant for hereditary angioedema. Drugs Today 2009;45(12):855-64.

64. Heymann WR, Moon A. Hereditary angioedema. In: eMedicine (now Medscape Reference) [internet]. New York (NY): WebMD, LLC; 2010 Aug 12 [accessed 2011 Jan 11]. [15 p]. Available: http://emedicine.medscape.com/article/1048994-overview.

65. Firazyr (icatibant) injection, for subcutaneous use prescribing information. [internet]. Lexington (MA): Shire Orphan Therapies, Inc.; 2011 Aug [accessed 2012 Apr 6]. [19 p]. Available: http://pi.shirecontent.com/PI/PDFs/Firazyr_USA_ENG.pdf.

66. Cicardi M, Banerji A, Bracho F, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. N Engl J Med 2010 Aug 5;363(6):532-41. PMID: 20818888

67. Self-administration of Firazyr (icatibant) for the treatment of acute hereditary angioedema (HAE) type I and II attacks, new data presented. [internet]. Bexhill-on-Sea (UK): Medical News Today LLC; 2011 Jun 22 [accessed 2011 Aug 10]. [5 p]. Available: http://www.medicalnewstoday.com/releases/229332.php.

68. Lumry WR, Li HH, Levy RJ, et al. Results from FAST-3: a phase III randomized, double-blind, placebo-controlled, multicenter study of subcutaneous icatibant in patients with acute hereditary angioedema (HAE) attacks. J Allergy Clin Immunol 2011 Feb;127(2 suppl):AB1. Also available: http://www.jacionline.org/article/S0091-6749(11)00040-6/fulltext.

69. FDA approves Shire's Firazyr (icatibant injection) for acute attacks of hereditary angioedema (HAE). [internet]. Dublin (Ireland): Shire plc; 2011 Aug 25 [accessed 2011 Oct 5]. [3 p]. Available: http://www.shire.com/shireplc/en/media/shirenews?id=520.

70. BioRx expands therapy offering to patients with hereditary angioedema. [internet]. Cincinnati (OH): BioRX; 2011 Sep 12 [accessed 2011 Sep 16]. [2 p]. Available: http://www.biorx.net/wp/wp-content/uploads/2011/09/firazyr-press-release-9-2011.pdf.

71. RxUSA.com [database online]. [accessed 2012 Oct 24]. Available: http://rxusa.com/cgi-bin2/db/db.cgi.

72. Aetna, Inc. Clinical policy bulletin: hereditary angioedema. Number: 0782. [internet]. Hartford (CT): Aetna, Inc.; 2011 Nov 15 [accessed 2012 Feb 9]. [9 p]. Available: http://www.aetna.com/cpb/medical/data/700_799/0782.html.

73. Anthem Blue Cross of California. Prescription program. Anthem Blue Cross California drug list. Woodland Hills (CA): Anthem Blue Cross of California; 2011 Oct. 8 p. Also available: http://www.anthem.com/CA.

74. Blue Cross Blue Shield of Alabama. Specialty pharmacy program drug list. East Birmingham (AL): Blue Cross Blue Shield of Alabama; 2012 Jan. 1 p. Also available: http://www.bcbsal.com.

75. CIGNA Corporation. Drug list search results: bradykinin B2 receptor antagonists. [internet]. Bloomfield (CT): CIGNA Corporation; [accessed 2012 Feb 9]. [1 p]. Available: http://www.cigna.com.

76. HealthPartners. Hereditary angioedema (HAE) drug therapy. Policy number H004-02. Minneapolis (MN): HealthPartners; 2011 Jan 1. 2 p. Also available: http://www.healthpartners.com/files/34431.pdf.

77. Humana, Inc. 2012 prescription drug guide Humana formulary [Region 21]. Louisville (KY): Humana, Inc.; 2011 Aug. 208 p. Also available: http://www.humana.com/.

78. Medica. Medica utilization management policy no. III-DRU-27. Icatibant (Firazyr). [internet]. Minnetonka (MN): Medica; 2011 Oct 5 [accessed 2012 Feb 9]. [2 p]. Available: http://www.medica.com.

79. RegenceRx. Medication policy manual: Firazyr, icatibant. Policy no: dru256. Portland (OR): RegenceRx; 2011 Nov 18. 5 p. Also available: http://blue.regence.com/trgmedpol/drugs/dru256.pdf.

80. UnitedHealthcare Oxford. Icatibant (Firazyr) policy #: PHARMACY 203.1 T2. Trumbull (CT): Oxford Health Plans, LLC; 2012 Feb 15. 2 p. Also available: https://www.oxhp.com/secure/policy/icatibant_firazyr.pdf.

81. Wellmark, Inc. Benefits enrollment guide [BlueAccess and BlueRx Preferred]. Des Moines (IA): Wellmark, Inc.; 2011 Nov 1. 84 p. Also available: http://www.wellmark.com.

82. Expert Commenter 396. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS652 - Icatibant (Firazyr) for treatment of acute hereditary angioedema. 2012 Oct 17 [review date].

83. Expert Commenter 408. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS652 - Icatibant (Firazyr) for treatment of acute hereditary angioedema. 2012 Oct 5 [review date].

84. Expert Commenter 423. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS652 - Icatibant (Firazyr) for treatment of acute hereditary angioedema. 2012 Sep 18 [review date].

85. Expert Commenter 433. (External, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS652 - Icatibant (Firazyr) for treatment of acute hereditary angioedema. 2012 Sep 19 [review date].

86. Expert Commenter 1173. (External, Clinical). Horizon Scanning Structured Comment Form. HS652 - Icatibant (Firazyr) for treatment of acute hereditary angioedema. 2012 Sep 26 [review date].

87. Expert Commenter 1193. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS652 - Icatibant (Firazyr) for treatment of acute hereditary angioedema. 2012 Sep 18 [review date].

88. Expert Commenter 1202. (External, Clinical). Horizon Scanning Structured Comment Form. HS652 - Icatibant (Firazyr) for treatment of acute hereditary angioedema. 2012 Oct 22 [review date].

89. Hemophilia: data and statistics. [internet]. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2010 July 2 [accessed 2010 Dec 21]. [13 p]. Available: http://www.cdc.gov/ncbddd/hemophilia/data.html .

90. Acquired hemophilia. Montreal (Quebec): World Federation of Hemophilia (WFH); 2005 Dec. 12 p. (Treatment of hemophilia; no. 38). Also available: http://www1.wfh.org/publication/files/pdf-1186.pdf.

91. Ipsen's partner Inspiration Biopharmaceuticals announces the treatment of the first patient in phase III pivotal study of OBI-1 for acquired hemophilia A. [internet]. Paris (France): Ipsen; 2010 Nov 19 [accessed 2010 Dec 21]. [2 p]. Available: http://www.ipsen.com/sites/default/files/communiques-presse/PR%20Ipsen%20-%20OBI%20phase%20III%20EN%20%20Final_1.pdf.

92. OBI-1 receives orphan drug designation in Europe. [internet]. Paris (France): Ipsen; 2010 Oct 19 [accessed 2010 Dec 21]. [2 p]. Available: http://www.ipsen.com/sites/default/files/communiques-presse/PR%20OBII-1%20orphan%20drug%20status%20granted%20by%20EC%20FINAL%20EN.pdf.

93. Inspiration Biopharmaceuticals announces data from OBI-1 pivotal-stage program in hemophilia at 23rd ISTH Congress. [internet]. Laguna Niguel (CA): Inspiration Biopharmaceuticals, Inc.; 2011 Jul 28 [accessed 2011 Aug 18]. [3 p]. Available: http://www.inspirationbio.com/files/994/60256.pdf.

94. Inspiration Biopharmaceuticals, Inc. Study of modified recombinant factor VIII (OBI-1) in subjects with congenital hemophilia A. In: Clinicaltrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2012 Nov 16]. [4 p]. Available: http://clinicaltrials.gov/ct2/show/NCT01434511 NLM Identifier: NCT01434511.

95. Ipsen's hemophilia partner, Inspiration Biopharmaceuticals, seeks Chapter 11 protection. [internet]. Paris: Ipsen; 2012 Oct 31 [accessed 2012 Nov 16]. [4 p]. Available: http://www.ipsen.com/sites/default/files/communiques-presse/PR%20Inspiration%20chapter%2011%20EN.pdf.

96. Inspiration Biopharmaceuticals files for Chapter 11 protection in order to pursue a broad strategic transaction. [internet]. Cambridge (MA): Inspiration Biopharmaceuticals, Inc.; 2012 Oct 31 [accessed 2012 Nov 16]. [2 p]. Available: http://www.inspirationbio.com/files/994/78825.pdf.

97. Expert Commenter 663. (External, Clinical). Horizon Scanning Structured Comment Form. HS435 - OBI-1 for treatment of acquired hemophilia. 2012 Apr 23 [review date].

98. Expert Commenter 428. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS435 - OBI-1 for treatment of acquired hemophilia. 2012 Apr 16 [review date].

99. Expert Commenter 447. (PRI, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS435 - OBI-1 for treatment of acquired hemophilia. 2012 Apr 26 [review date].

100. Expert Commenter 400. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS435 - OBI-1 for treatment of acquired hemophilia. 2012 Apr 23 [review date].

101. Expert Commenter 1015. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS435 - OBI-1 for treatment of acquired hemophilia. 2012 Apr 19 [review date].

102. Expert Commenter 1173. (PRI, Clinical). Horizon Scanning Structured Comment Form. HS435 - OBI-1 for treatment of acquired hemophilia. 2012 Apr 18 [review date].

103. Migraine headache. [internet]. San Clemente (CA): MedicineNet, Inc.; [accessed 2012 Apr 11]. [12 p]. Available: http://www.medicinenet.com/script/main/art.asp?articlekey=417&pf=3&page=1.

104. Silberstein SD, Kori SH, Aurora SK, et al. Efficacy and tolerability of MAP0004, a novel inhaled therapy, in treating acute migraine. [internet]. Mountain View (CA): MAP Pharmaceuticals, Inc.; 2009 Sep 10 [accessed 2011 Jan 6]. [1 p]. Available: http://www.mappharma.com/file.cfm/124/docs/MAP-IHC_Poster1_Web.pdf.

105. Buck ML. Intravenous dihydroergotamine for the treatment of refractory migraines. In: Medscape Today [internet]. New York (NY): WebMD, LLC; 2007 Aug 20 [accessed 2011 Jan 6]. [6 p]. Available: http://www.medscape.com/viewarticle/561217.

106. Thomson Reuters Pharma [database online]. Thomson Reuters; [updated 2010 Dec 22]; [accessed 2010 Dec 27]. Dihydroergotamine (migraine, Tempo-inhaled/oral), MAP. [10 p]. Available: https://www.thomson-pharma.com.

107. Science and technology. [internet]. Mountain View (CA): MAP Pharmaceuticals, Inc.; [accessed 2011 Jan 6]. [1 p]. Available: http://www.mappharma.com/ScienceandTechnology/.

108. Rapoport AM. New acute treatments for headache. Neurol Sci 2010 Jun;31 Suppl 1:S129-32. PMID: 20464603

109. Aurora SK, Silberstein SD, Kori SH, et al. MAP0004, orally inhaled DHE: a randomized, controlled study in the acute treatment of migraine. Headache 2011 Apr;51(4):507-17. PMID: 21457235

110. MAP Pharmaceuticals receives complete response letter from FDA for Levadex (dihydroergotamine) NDA. [internet]. Mountain View (CA): MAP Pharmaceuticals, Inc.; 2012 Mar 26 [accessed 2012 Apr 11]. [2 p]. Available: http://ir.mappharma.com/releasedetail.cfm?ReleaseID=659519.

111. MAP Pharmaceuticals resubmits New Drug Application to FDA for Levadex orally inhaled migraine drug. [internet]. Mountain View (CA): MAP Pharmaceuticals, Inc.; 2012 Oct 16 [accessed 2012 Nov 13]. [1 p]. Available: http://ir.mappharma.com/releasedetail.cfm?ReleaseID=713682.

112. Expert Commenter 401. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS367 - LEVADEX (MAP-0004) orally inhaled treatment for migraine headaches. 2012 Oct 5 [review date].

113. Expert Commenter 671. (External, Clinical). Horizon Scanning Structured Comment Form. HS367 - LEVADEX (MAP-0004) orally inhaled treatment for migraine headaches. 2012 Sep 19 [review date].

114. Expert Commenter 447. (External, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS367 - LEVADEX (MAP-0004) orally inhaled treatment for migraine headaches. 2012 Oct 17 [review date].

115. Expert Commenter 1026. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS367 - LEVADEX (MAP-0004) orally inhaled treatment for migraine headaches. 2012 Oct 5 [review date].

116. Expert Commenter 524. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS367 - LEVADEX (MAP-0004) orally inhaled treatment for migraine headaches. 2012 Sep 17 [review date].

117. Expert Commenter 489. (External, Clinical). Horizon Scanning Structured Comment Form. HS367 - LEVADEX (MAP-0004) orally inhaled treatment for migraine headaches. 2012 Sep 10 [review date].

118. Expert Commenter 397. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS367 - LEVADEX (MAP-0004) orally inhaled treatment for migraine headaches. 2012 Sep 18 [review date].

119. Schneider EW, Johnson MW. Emerging nonsurgical methods for the treatment of vitreomacular adhesion: a review. Clin Ophthalmol 2011;5:1151-65. PMID: 21887098

120. Bhisitkul RB. Anticipation for enzymatic vitreolysis. Br J Ophthalmol 2001 Jan;85(1):1-2. Also available: http://bjo.bmj.com/content/85/1/1. PMID: 11133700

121. Ocriplasmin. [internet]. Heverlee (Belgium): ThromboGenics NV [accessed 2012 Mar 23]. [2 p]. Available: http://thrombogenics.com/our-science/ophthalmology/ocriplasmin/.

122. Johnson MW. Perifoveal vitreous detachment and its macular complications. Trans Am Ophthalmol Soc 2005;103:537-67. Also available: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1447588/. PMID: 17057817

123. ThromboGenics NV. ThromboGenics' microplasmin phase III program progressing according to schedule. [internet]. Bio-Medicine; 2009 Jun 24 [accessed 2011 Jan 11]. Available: http://www.bio-medicine.org/medicine-technology-1/ThromboGenics-Microplasmin-Phase-III-Program-Progressing-According-to-Schedule-4647-1/.

124. Williams GA. Enzymatic vitreolysis for retinal disorders. Rev Ophthalmol 2008 May 1;15(5) Also available: http://www.revophth.com/index.asp?page=1_13827.htm.

125. de Smet MD, Valmaggia C, Zarranz-Ventura J, et al. Microplasmin: ex vivo characterization of its activity in porcine vitreous. Invest Ophthalmol Vis Sci 2009 Feb;50(2):814-9. Also available: http://www.iovs.org/content/50/2/814.full. PMID: 18806295

126. ThromboGenics presents positive pooled results from the MIVI-TRUST phase III program, confirming microplasmin's potential to transform the treatment of retinal disorders. Heverlee (Belgium): ThromboGenics NV; 2010 Sep 6. 4 p. Also available: http://www.thrombogenics.com/html/documents/10_THR_16MicroplasminPooledResults_FINAL_EN.pdf.

127. Intravitreal injection. [internet]. Philadelphia (PA): Mid Atlantic Retina and MedNet Technologies, Inc. [accessed 2011 Jan 11]. [2 p]. Available: http://www.midatlanticretina.com/intravitreal-injection.php.

128. ThromboGenics presents positive pooled results from the MIVITRUST phase III program, confirming microplasmin's potential to transform the treatment of retinal disorders. [internet]. Leuven (Belgium): ThromboGenics NV; 2010 Sep 6 [accessed 2011 Aug 15]. [4 p]. Available: http://thrombogenics.com/wp-content/uploads/documents/10_THR_16MicroplasminPooledResults_FINAL_EN.pdf.

129. ThromboGenics submits biologics license application for ocriplasmin to the U.S. FDA. [internet]. Heverlee (Belgium): ThromboGenics NV; 2011 Dec 23 [accessed 2012 Mar 22]. [2 p]. Available: http://thrombogenics.com/wp-content/uploads/2011/03/11_THR_18-Ocriplasmin-US-filing-Final-ENG2.pdf.

130. ThromboGenics announces that the FDA intends to grant ocriplasmin priority review. [internet]. Heverlee (Belgium): ThromboGenics NV; 2012 Feb 2 [accessed 2012 Mar 22]. [2 p]. Available: http://thrombogenics.com/wp-content/uploads/2011/03/THR_02_Ocriplasmin-BLA-Priority-Review_Final_ENG.pdf.

131. U.S. Food and Drug Administration (FDA). FDA approves Jetrea for symptomatic vitreomacular adhesion in the eyes. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2012 Oct 18 [accessed 2012 Oct 24]. [2 p]. Available: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm324369.htm.

132. U.S. FDA approves ThromboGenics' JETREA (ocriplasmin) for the treatment of symptomatic vitreomacular adhesion (VMA). [internet]. Leuven (Belgium): ThromboGenics; 2012 Oct 18 [accessed 2012 Nov 16]. [4 p]. Available: http://thrombogenics.com/wp-content/uploads/2011/03/THR-FDA-JETREA-approval.pdf.

133. Stalmans P. Management and intervention strategies for symptomatic vitreomacular adhesions. Retinal Physician 2011 May. Also available: http://thrombogenics.com/wp-content/uploads/2011/05/May_Retinal-Physician_Stalmans.pdf.

134. Expert Commenter 1171. (External, Clinical). Horizon Scanning Structured Comment Form. HS420 - Recombinant human microplasmin injection for treatment of focal vitreomacular adhesion. 2012 Oct 17 [review date].

135. Expert Commenter 428. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS420 - Recombinant human microplasmin injection for treatment of focal vitreomacular adhesion. 2012 Sep 13 [review date].

136. Expert Commenter 397. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS420 - Recombinant human microplasmin injection for treatment of focal vitreomacular adhesion. 2012 Sep 18 [review date].

137. Expert Commenter 408. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS420 - Recombinant human microplasmin injection for treatment of focal vitreomacular adhesion. 2012 Oct 5 [review date].

138. Expert Commenter 144. (External, Clinical). Horizon Scanning Structured Comment Form. HS420 - Recombinant human microplasmin injection for treatment of focal vitreomacular adhesion. 2012 Sep 20 [review date].

139. Expert Commenter 1192. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS420 - Recombinant human microplasmin injection for treatment of focal vitreomacular adhesion. 2012 Sep 13 [review date].

140. ReWalk: general description. [internet]. Yokneam Ilit (Israel): Argo Medical Technologies, Ltd. [accessed 2011 Jan 25]. [2 p]. Available: http://www.argomedtec.com/products.asp.

141. Ekso Bionics delivers first "Ekso" exoskeleton. [internet]. Berkeley (CA): Ekso Bionics; 2012 Feb 15 [accessed 2012 Mar 30]. [3 p]. Available: http://www.eksobionics.com/blog/2012/02/ekso-bionics-delivers-first-ekso-exoskeleton/.

142. Ekso product overview. [internet]. Berkeley (CA): Ekso Bionics [accessed 2012 Mar 30]. [2 p]. Available: http://www.eksobionics.com/data/downloads/Ekso_Specs.pdf.

143. Establishment registration & device listing: ReWalk-I. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2011 Nov 7 [accessed 2011 Nov 16]. [1 p]. Available: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRL/rl.cfm?lid=260402&lpcd=BXB.

144. Technology review – ReWalk. [internet]. Toronto (ON): Neurochangers; 2011 Aug 12 [accessed 2012 Mar 30]. [5 p]. Available: http://neurochangers.com/2011/08/12/technology-review-rewalk/.

145. Ekso's exoskeletons let paraplegics walk. Now all it has to do is convince the world they're necessary. [internet]. New York (NY): Fast Company; 2012 Mar 19 [accessed 2012 Mar 30]. [8 p]. Available: http://www.fastcompany.com/magazine/164/ekso-bionics.

146. Living with spinal cord injury (SCI). [internet]. Bethesda (MD): The American Occupational Therapy Association, Inc. ; 2007 May 16 [accessed 2011 Jan 25]. [1 p]. Available: http://www.aota.org/Consumers/consumers/Health-and-Wellness/SCI/35189.aspx.

147. Expert Commenter 1193. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS657 - Reciprocating gait orthosis (computerized walking system) for paraplegia from spinal cord injury. 2012 Jul 31 [review date].

148. Expert Commenter 64. (External, Clinical). Horizon Scanning Structured Comment Form. HS657 - Reciprocating gait orthosis (computerized walking system) for paraplegia from spinal cord injury. 2012 Aug 31 [review date].

149. Expert Commenter 398. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS657 - Reciprocating gait orthosis (computerized walking system) for paraplegia from spinal cord injury. 2012 Aug 6 [review date].

150. Expert Commenter 427. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS657 - Reciprocating gait orthosis (computerized walking system) for paraplegia from spinal cord injury. 2012 Aug 6 [review date].

151. Expert Commenter 539. (External, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS657 - Reciprocating gait orthosis (computerized walking system) for paraplegia from spinal cord injury. 2012 Aug 29 [review date].

152. Expert Commenter 982. (External, Research/Scientific/Technical). Horizon Scanning Structured Comment Form. HS657 - Reciprocating gait orthosis (computerized walking system) for paraplegia from spinal cord injury. 2012 Aug 29 [review date].

153. Expert Commenter 1015. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS657 - Reciprocating gait orthosis (computerized walking system) for paraplegia from spinal cord injury. 2012 Aug 9 [review date].

154. Georgia Institute of Technology. Evaluation of a tongue operated assistive technology for individuals with severe paralysis (TDS-1). In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2011 Oct 3]. [8 p]. Available: http://clinicaltrials.gov/ct2/show/NCT01124292 NLM Identifier: NCT01124292.

155. Mouth gear: tongue drive system goes inside the mouth to improve performance and user comfort. [internet]. Atlanta (GA): Georgia Institute of Technology [accessed 2012 Nov 16]. [3 p]. Available: http://gtresearchnews.gatech.edu/tonguedrive3/.

156. Tongue drive system lets persons with disabilities operate powered wheelchairs, computers. [internet]. Rockville (MD): ScienceDaily; 2008 Jun 30 [accessed 2011 Oct 3]. [3 p]. Available: http://www.sciencedaily.com/releases/2008/06/080630090821.htm.

157. Tongue power: clinical trial shows quadriplegic individuals can operate powered wheelchairs and computers with tongue drive system. [internet]. Atlanta (GA): Georgia Institute of Technology; 2009 Jul 6 [accessed 2011 Oct 3]. [2 p]. Available: http://gtresearchnews.gatech.edu/newsrelease/tonguedrive2.htm.

158. Expert Commenter 404. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS1157 - Magnetic tongue-piercing aid for management of spinal cord paralysis. 2011 Oct 24 [review date].

159. Expert Commenter 484. (External, Clinical). Horizon Scanning Structured Comment Form. HS1157 - Magnetic tongue-piercing aid for management of spinal cord paralysis. 2011 Oct 25 [review date].

160. Expert Commenter 64. (External, Clinical). Horizon Scanning Structured Comment Form. HS1157 - Magnetic tongue-piercing aid for management of spinal cord paralysis. 2012 Apr 5 [review date].

161. Expert Commenter 421. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1157 - Magnetic tongue-piercing aid for management of spinal cord paralysis. 2012 Apr 10 [review date].

162. Expert Commenter 416. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1157 - Magnetic tongue-piercing aid for management of spinal cord paralysis. 2012 Apr 10 [review date].

163. Expert Commenter 1174. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS1157 - Magnetic tongue-piercing aid for management of spinal cord paralysis. 2012 Apr 10 [review date].

164. Expert Commenter 539. (External, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS1157 - Magnetic tongue-piercing aid for management of spinal cord paralysis. 2012 Apr 19 [review date].

165. Expert Commenter 541. (External, Research/Scientific/Technical). Horizon Scanning Structured Comment Form. HS1157 - Magnetic tongue-piercing aid for management of spinal cord paralysis. 2012 Apr 25 [review date].

166. Expert Commenter 400. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS1157 - Magnetic tongue-piercing aid for management of spinal cord paralysis. 2012 Apr 24 [review date].